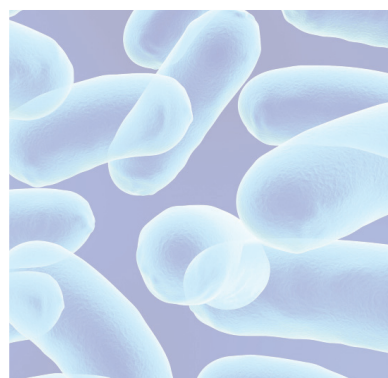


An International Roadmap for Tuberculosis Research



Towards a world free of tuberculosis

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ABBREVIATIONS

AIDS	Acquired Immunodeficiency Syndrome
ART	Antiretroviral therapy
BCG	Bacillus Calmette-Guérin
DOTS	Directly observed treatment, short course
DST	Drug sensitivity testing
HIV	Human immunodeficiency virus
IPT	Isoniazid preventive therapy
LTBI	Latent tuberculosis infection
MDR	Multidrug-resistant
NAAT	Nucleic acid amplification tests
NGO	Nongovernmental organizations
PLHIV	People living with HIV/AIDS
TB	Tuberculosis
XDR	Extensively drug-resistant

FOREWORD

Elimination of tuberculosis (TB) is more than an aspiration. We know it could become a reality, but this will happen only if we achieve radical transformation in the way TB is diagnosed, treated and prevented. This goal can be realized only if TB research is intensified and envisioned in an entirely new way. It must be viewed as a continuum from basic research (for discovery) to operational research (to achieve optimal implementation).

New technologies are needed for optimal prevention, diagnosis and treatment of all forms of TB in people of all ages, including those living with HIV. Such tools must deliver quicker results, be affordable to the poor and applied in combination to secure public health impact and simplified management of TB control. These advances will require a quantum leap in our understanding of fundamental TB science, leading to reinvigorated research and development of new diagnostics, drugs and vaccines, coupled with novel health system designs that advance the adoption and diffusion of new technologies.

Achieving these goals also will require a revolution in the way researchers on TB harmonize their efforts. We believe this publication will provide scientists around the world with a common framework for collaboration. It encompasses all aspects of research that need to be conducted, from basic science and discovery to development of new diagnostics, drugs and vaccines and their optimal uptake for better TB care and control. It has been developed through a series of meetings and workshops assembling a diverse group of TB research

stakeholders, who together identified and prioritized the critical questions that must be addressed for the transformational research that is indispensable to make our world free of TB.

The roadmap is the product of the Research Movement, created by the Stop TB Partnership and the WHO Stop TB Department in 2006 to address the urgent need for increased commitment for TB research. The Research Movement is intended to provide leadership and advocacy to mobilize increased resources in support of a coherent and comprehensive global TB research agenda to meet the Stop TB goals and targets; and to provide a forum for TB researchers and funders of TB research to coordinate priorities and actions. The roadmap represents the critical next step in the Research Movement strategy, building on of the Stop TB Partnership's Global Plan to Stop TB 2011–2015: Transforming the Fight - Towards elimination of Tuberculosis.

Ultimately, the objective of TB research is to ensure a better future for women, men and children all over the world. The Stop TB Partnership is united in advocating for increased and harmonized investment in scientific research on TB to fortify the foundations of knowledge that will lead to life-saving innovations.

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PREFACE

Tuberculosis is still, in the early part of the 21st century, a major cause of morbidity and deaths, a disease that humanity is struggling to control and the consequences of which have caused, and are still causing, immense suffering. Over the past decade and a half, WHO has focused its approach to this global public health issue by promoting a comprehensive strategy to care and control, lately described as Stop TB Strategy. Thanks to its intensive implementation, achievements have been remarkable in nearly all countries world-wide. However, despite these encouraging results, the TB epidemic is not being eliminated as a public health problem, as revealed by the very slow incidence decline (estimated at 1.3% per year), the high mortality world-wide, the delays in diagnosis that perpetuate transmission in the community, and the 90% of MDR-TB cases that are not on proper treatment. Thus, in 2011, a four-pronged approach is necessary to achieve better control and seriously target TB elimination.

First, TB control programmes must optimize diagnosis, treatment and care of cases as described in the Stop TB Strategy and as promoted in the Stop TB Partnership Global Plan to Stop TB 2011-2015.

Second, bold policies across health system and services, both public and non-state, are crucial to allow core TB interventions to be effective.

Third, correction of the main risk factors for TB and alleviation of the social and economic determinants of ill health are paramount to accelerate impact of planned efforts.

Finally, research, the fourth component of our modern approach, is a fundamental means to maximize the advances already achieved in TB control through strengthening of programmes and health services, and alleviation of risks and determinants. Current tools that are widely used in TB high-burden countries are not the ideal ones to reduce deaths effectively and contain the TB epidemic. Of all four measures promoted, research is the key milestone for any attempt to impact on incidence in a substantive way.

During the past years, the attention of the international TB community has been called on the need to establish a priority agenda for research needed to quickly improve delivery of care to all affected by TB. Thanks to the umbrella offered by the Research Movement, it has been possible to put around the table all major stakeholders in TB research, thus progressing jointly in the thinking towards a united front that promotes, describes and encourages massively increased investments in TB research.

Following the recent publication of the “Priorities in operational research to improve tuberculosis care and control”, this new publication constitutes the necessary “international roadmap” that should stipulate the pragmatic principles of effective research efforts in TB. The key research questions have been determined through a sound and comprehensive approach engaging all those who could contribute innovative ideas. They have been compiled carefully to reflect the sentiments of all experts and passionate supporters of research in TB. They have been ultimately grouped by main area of work, avoiding competition between different aspects of research, and advocating in fact for all areas to be supported. TB research efforts cannot afford unfair internal competition in this era of financial uncertainties. Rather, the entire TB community must never cease to emphasize that research begins in the laboratory and ends at the bed side of a poor person affected by a disease that we should be able to prevent with all our technology and capacity in the 21st century. Yet, this is not the case: one more reason to work jointly, all of us at WHO, governments, NGOs, civil society, research institutions, and advocate for more investments in the priority areas that we have agreed upon. The Roadmap intends to facilitate this effort and must be looked at as the way forward to achieve real progress in TB care, control and prevention that will benefit humanity for generations to come.

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EXECUTIVE SUMMARY

Tuberculosis (TB) remains an unacceptable burden, causing human suffering and loss that overwhelmingly affects poor and vulnerable people living in low- and middle-income countries. The low decline in the estimated incidence of TB observed since 2004 is insufficient to reach the global target of elimination, defined as one or less case of TB per million population per year, by 2050. Major progress in global TB control will be achieved only if highly effective, widely accessible tools for the prevention, diagnosis and treatment of TB become available in reinforced health systems and are associated with strategies targeting the social and economic determinants of the disease.

A profound expansion of the fundamental science is necessary to develop revolutionary new technologies and novel service delivery models, along with novel evidence-based health system designs that foster adoption and diffusion of new tools and technologies. This will require proactive coordination of plans and actions to ensure that key research needs are being addressed, opportunities identified and prioritized and gaps filled. It is this view that inspired the creation of the TB Research Movement by the Stop TB Partnership and WHO, with the aim of vigorously stimulating, supporting and expanding research to ensure progress towards the elimination of TB as a global public health problem by 2050.

In September 2009, the TB Research Movement started a process leading to the development of a comprehensive roadmap for global TB research. The objective was to identify the key research questions to achieve TB elimination by 2050, and thus the key areas in which to encourage investment, with a view to enhancing and harmonizing funding across the research spectrum and providing basis for better coordination of research.

The **method** used to develop this roadmap relied on the combination of:

- a several-stage Delphi technique, involving multidisciplinary stakeholders;
- a series of systematic reviews;
- an open web-based survey; and
- a clear, transparent, objectively measurable priority ranking exercise, conducted by a group of 50 multidisciplinary research experts.

Based on these, the roadmap presents a coherent list of priorities for research over the next 5–15 years and key questions for the development of better tools for improved TB control. Research priorities are identified in the areas of: epidemiology, fundamental research, research and development of new diagnostics, drugs and vaccines, and operational and public health research.

Epidemiology

Epidemiological research is fundamental to understand the causes and distribution of TB in populations, especially high-risk groups, and identification of areas for targeted intervention; it is also of value for all other research areas.

The main priorities include:

- sustained measurement of the burden of disease and of variations in the dynamics of TB in various settings;
- identification of the causes of low rates of case detection and cure, especially in certain high-risk groups and settings;
- identification of the biological, environmental, population-based and social drivers of transmission of *Mycobacterium tuberculosis* and investigation of the relative contributions of different foci of TB transmission in the population; and
- better understanding of the interaction between the pathogen, the host and the social determinants of *M. tuberculosis* transmission in specific settings and in high-risk populations, including people coinfecting with TB and human immunodeficiency virus (HIV), and patients with multidrug-resistant (MDR) and extensively drug-resistant (XDR) TB.

Fundamental research

Key aspects of fundamental research for the development of new tools and strategies for better TB control are the better characterization of human TB, the better understanding of the various stages of TB disease progression and the identification of the stage-specific markers of this progression.

The main research priorities are:

- better understanding of the host–pathogen interaction, particularly the mechanisms leading to persistence or elimination of the bacilli in relation to different host conditions (e.g., age, HIV coinfection);
- better understanding of the interaction of *M. tuberculosis* with the immune system during progression from infection to disease;
- identification of the respective components of the host's immune system and of the pathogen that are critical for elimination of *M. tuberculosis* and/or for preventing reactivation of latent TB infection, including the role of mucosal immunity; and
- identification of biomarkers (or combinations of markers) that distinguish the stages of TB across the spectrum and allow accurate identification of patients at each stage.

Research and development of new diagnostics

The main goal is to increase TB case detection through new and improved diagnostics to detect active disease at point-of-care level, diagnose latent TB infection and predict disease progression, and rapidly screen and diagnose multidrug- and extensively drug-resistant TB, HIV-associated TB and paediatric TB.

The key research areas are:

- evaluation of biomarkers identified in fundamental studies for use as diagnostic tools; and
- validation of novel simple tools for diagnosis at points of care.

The main priorities include:

- identification of a systemic marker of bacterial load in various samples and with various methods;
- definition and evaluation of the accuracy of new diagnostic tests;
- identification of the best methods for determining the impact of improved or new diagnostic tools at patient, population and health system levels, including feasibility, cost-effectiveness, diagnostic delay, clinical decision-making and patient benefit; and

- identification of the best combination(s) of existing and new diagnostics for optimizing detection of the various forms and types of TB (drug-sensitive and drug-resistant, pulmonary and extrapulmonary, and latent TB infection) in various populations (such as children and people living with HIV) and at all health-care levels.

Research and development of new drugs

The main goal is to develop shorter TB regimens to cure all forms of TB that are safe, compatible with antiretroviral therapy (ART), suitable for children, effective against latent tuberculosis infection, affordable, easily managed in the field and that remain effective by limiting the development of drug resistance. Prominent fundamental research areas in the development of new drugs include:

- design of systems biology models of *M. tuberculosis* metabolism and physiology to facilitate modern cell- and target-based drug discovery;
- better understanding or identification of the mechanisms of action of current and newly developed anti-TB drugs; and
- better understanding of TB persistence.

The key research priorities are:

- development of new TB drugs (optimal dosage, safety and efficacy) and their interaction with other (TB and non-TB) drugs; and
- identification of optimal treatment regimens for all populations (i.e. patients with drug-sensitive and drug-resistant TB, patients with TB–HIV coinfection and children).

The main priorities include:

- identification of the best methods for determining optimal combination(s) of drugs as early as possible in the overall drug development (for both drug-sensitive and drug-resistant TB);
- identification of the best models of testing for investigating drug combination regimens (including fixed-dose combinations) and interactions between TB drugs and other drugs (such as antiretroviral agents), and the effect of intercurrent conditions (such as malnutrition);

- identification of biomarker(s) (or combinations of) that will help in measuring the treatment effect that correlates with bactericidal and sterilizing activities of tested drugs, in order to shorten the duration of clinical trials; and
 - determination of optimal TB preventive therapy (efficacy, safety, tolerability and duration of protection) that can be used in HIV-infected adults and children, particularly those receiving antiretroviral therapy (ART).
- the optimal conditions of use (duration of intervals, boosting dose and number of boosts);
 - development of standardized assays to assess vaccine-induced immunogenicity to allow better comparison of candidate vaccines in different settings;
 - conduct of prevaccine epidemiological studies to facilitate TB vaccine development and implementation of vaccine trials; and
 - identification of suitable methods for standardizing and planning trial sites and protocols.

Research and development of new vaccines

Fundamental research questions for vaccine development include identification of the components of the host immune system that are critical for the control and elimination of TB bacilli. This involves determining the respective roles of innate and adaptive immunity in preventing *M. tuberculosis* infection and reactivation of latent disease, and better understanding of the immune response to different metabolic stages of the pathogen in various populations (e.g. according to HIV infection status and age, from infancy to adolescence and adulthood).

The key research areas are:

- identification of immunodominant antigens (or their components) that could be added to vaccines to increase protection;
- identification of correlates of protective immunity after vaccination;
- determination of appropriate clinical end-points and immunological read-outs for vaccine trials (especially in children); and
- identification of novel model systems for preclinical and clinical (challenge model) testing of TB vaccines, including pre- and post-exposure models and models to mimic reactivation.

The main priorities include:

- better understanding of the immune responses to new vaccines and bacillus Calmette-Guérin (BCG), both in animal models and in different human populations and age groups;
- development of improved vaccines for prime–boost vaccination (including improvement of BCG as a prime) and

Operational and public health research

High-priority operational research questions relate to TB case-finding, screening, access to diagnostics, treatment access and delivery, interactions between TB and HIV control programmes and infection control. These areas must be addressed in the context of both general health services and for high-risk groups (e.g. people with TB–HIV coinfection, those with MDR-TB, children and prisoners).

The areas of highest priority are:

- optimization of TB case-finding, particularly in HIV-infected and other vulnerable populations (e.g. identification of the best screening algorithms, improved access to diagnostic services, etc.);
- expanded access to treatment for vulnerable and marginalized groups by involving private and alternative health-care providers;
- strategies to scale up diagnosis of and access to treatment for MDR-TB and XDR-TB in resource-limited settings;
- strategies to scale up isoniazid preventive therapy (IPT) under field conditions and in HIV clinics delivering ART;
- strengthened integration of TB and HIV interventions; and
- methods to better implement, monitor and evaluate TB infection control in health settings, communities and households.

Note

In this document, aspects of research specifically related to TB–HIV co-infection, MDR-TB or

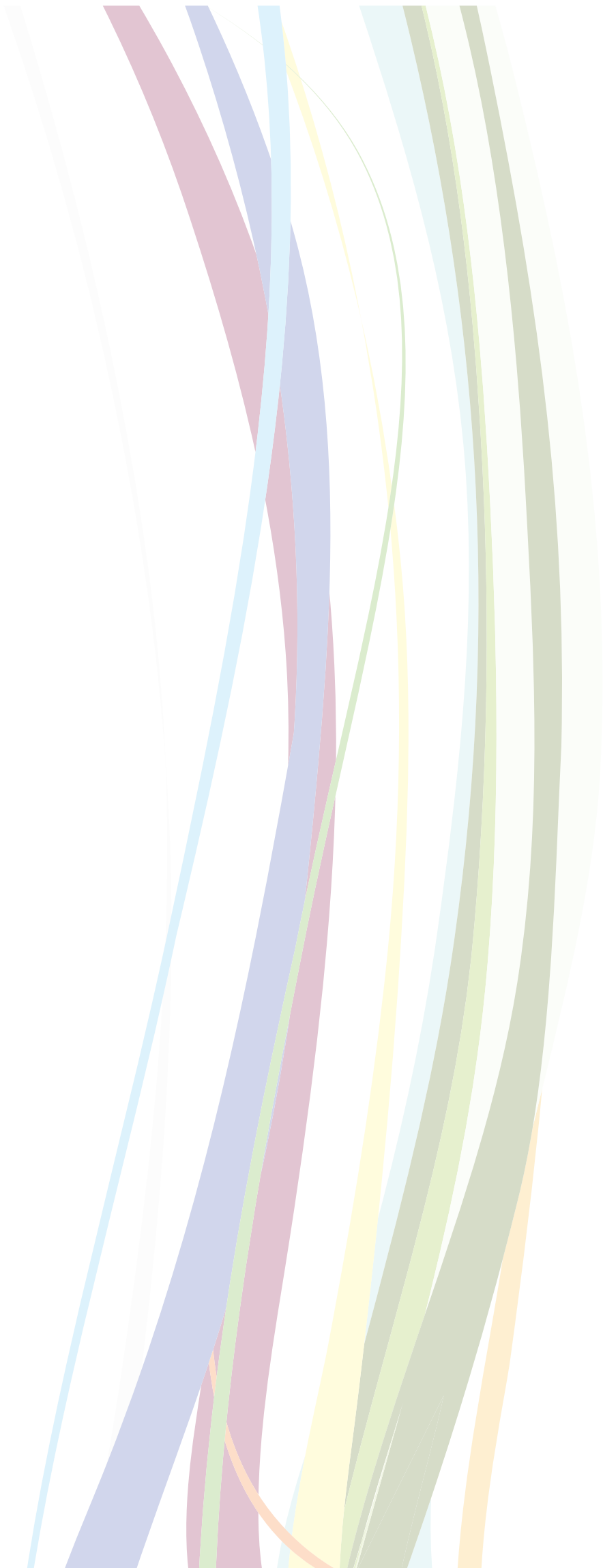
paediatric TB are systematically addressed within each of the areas defined above. In addition, this document does not propose methods or protocols for addressing the research priorities identified, as these depend on the specific question and often on the context. Nonetheless, as many of the main research questions require data on humans and biological specimens, designs for collecting such data and materials can be proposed for use in multidisciplinary approaches. An ideal design would feature large-scale, multi-site, longitudinal studies conducted in populations in high exposure settings and in groups at high risk for disease progression (i.e. children under 5 years, household TB contacts, HIV infected persons). Fully characterized specimens would be collected from these people at various stages of infection and disease for microbial and host biomarker studies.

Conclusion

The questions listed in this document are complex and can be addressed only by close coordination and collaboration among all stakeholders, across disciplines and across settings. This document lists

the essential research questions that will provide a common framework for various scientific disciplines to work concurrently and collaboratively towards better TB control and elimination. Responses to these questions are expected to fill knowledge gaps and indicate ways to develop and use new, safe, effective, accessible and affordable tools for the control of TB, so as to best prevent, detect and treat TB in all populations (including those with TB–HIV co-infection or MDR-TB and paediatric populations). This will require fine coordination of plans and actions to ensure that key research needs are being addressed, opportunities prioritized and gaps filled.

The aim of the present document is to ensure that research is promoted worldwide, including in low-income countries, which bear the largest burden of human suffering due to TB, and that appropriate technology is transferred so that novel control tools become accessible and affordable to populations in the countries that need them most. These are critical steps for achieving elimination of TB as a public health problem by 2050.



I. INTRODUCTION

The need for accelerated and better funded research for tuberculosis

The estimated incidence of TB has been declining globally since 2004; however, the present rate of decline, less than 1% per year, is insufficient to reach the global target of elimination, defined as one case of TB or less per million population per year, by 2050 (1). With 9.4 million new cases of TB and 1.7 million deaths from TB worldwide in 2009, the disease represents an unacceptable burden of human suffering and loss, overwhelmingly borne by poor and vulnerable people living in low- or middle-income countries. Progress in global TB control is constrained, however, by lack of highly effective, widely accessible diagnostics, drugs and vaccines; by the weakness of many health systems, which fail to deliver prompt, effective diagnosis and treatment with the existing tools; and a dearth of strategies to address the social and economic antecedents of the disease. Revolutionary new technology and service delivery models are needed to achieve elimination of TB by 2050. This requires an intensification of research across the continuum, from fundamental research for better understanding of human TB and discovery of new diagnostics, drugs and vaccines, to operational research for the introduction of new tools and better use of existing tools for prevention and treatment of TB. For optimal effectiveness, investment in research must be coupled with a readiness to rapidly adopt and implement policies based on new scientific evidence.

In view of the importance of research for accelerating progress towards achieving the goal of TB elimination by 2050, the Stop TB Partnership and the WHO Stop TB Department established in 2007 the TB Research Movement, with the overall goal of vigorously stimulating, supporting and expanding research (2). The role of the Movement is to identify areas in which substantial progress is needed to overcome the scientific challenges to the development of new diagnostics, drugs and vaccines to improve efficacy beyond the current standard of care, along with an appropriate transfer of technology to high-burden countries using best-practice models in different settings. The standards of care are unlikely to improve without better understanding of the social context of tuberculosis to better explain why people do and do not engage with their local health services when they are sick, and to understand the behaviour, practices

and attitudes of health-care practitioners (3). The broad policy arena must also be understood if new policies and solutions are to be adopted and owned locally within complex, overstretched health systems.

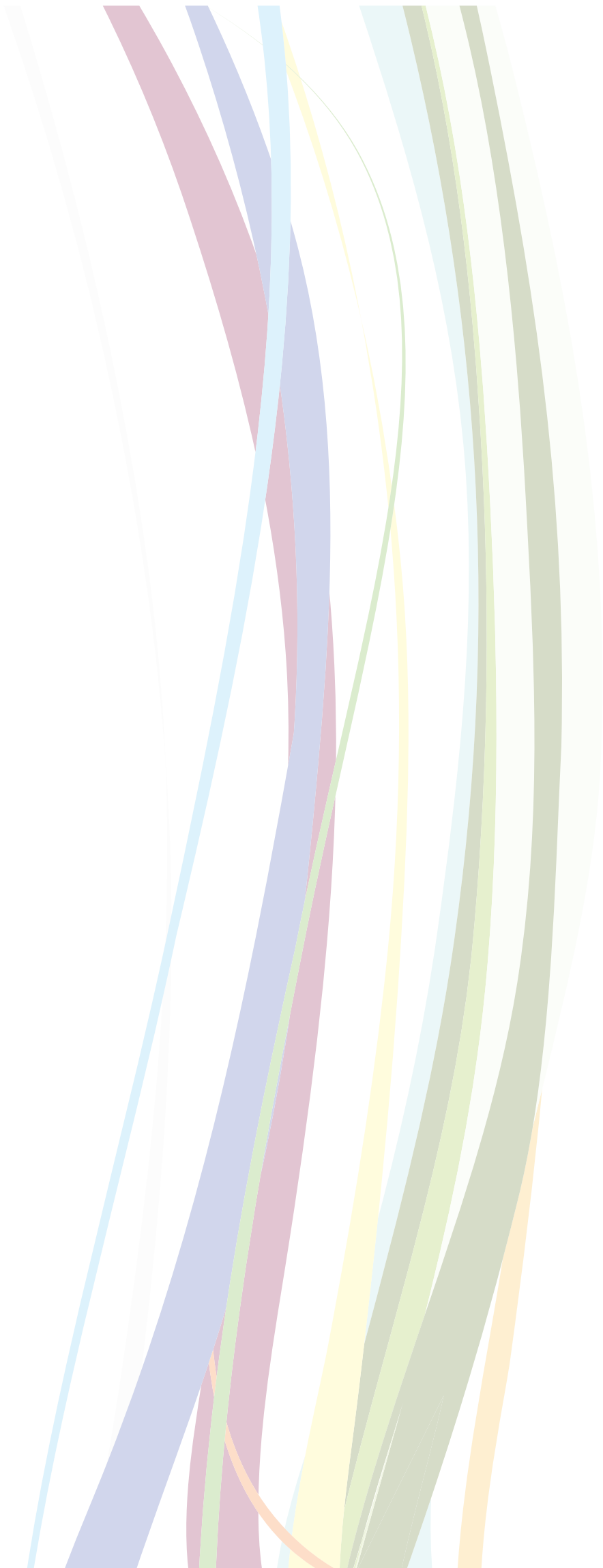
Elimination of TB by 2050 can only be achieved through a profound expansion of the fundamental science that is necessary to understand TB and that underpins the discovery and development of new diagnostics, drugs and vaccines, along with new evidence-based health system designs that foster adoption and diffusion of both new and existing tools and technologies. This will demand proactive coordination of plans and actions to ensure that key research needs are being addressed, opportunities identified and prioritized, and gaps filled.

According to the 2010 report of the Treatment Action Group (4), global financing for TB research and development increased by 72% between 2005 and 2009, from US\$ 357 million to US\$ 614 million. This sum is, however, far less than that required to sustain development and delivery of more effective tools to control and eliminate TB. The *Global Plan to Stop TB 2006–2015* called for funding of US\$ 56 billion for the 10-year period, including US\$ 11 billion for research and development. The updated *Global Plan to Stop TB 2011–2015* calls for an estimated US\$ 47 billion for the next 5 years (US\$ 16 billion more than 2006 projections), including US\$ 9.8 billion for research and development, i.e. nearly a doubling of investment (5). For the first time, the Plan includes the topic of fundamental research, reflecting the need to increase integration of biomedical sciences into TB care and control. Operational research is also included as a distinct topic because of its essential role in improving TB control programme activities, at the interface between the development of new tools and their uptake by national TB control programmes. This invigorated Plan reflects the need to extend the current focus on research and development to push for elimination. It is essential to mobilize funds to increase knowledge about human TB, so that a steady influx of candidate products enters clinical development for improved diagnosis, treatment and prevention and that these novel technologies are used and delivered under programme conditions in the most cost-effective way.

A global TB research roadmap

In September 2009, the TB Research Movement began to mobilize a broad alliance of stakeholders in fundamental, product development and operational research on TB, including academia, research institutions, national TB control programmes, public–private partnerships, public and private funding institutions, nongovernmental organizations, bilateral and international organizations and patients’ representatives (all subsequently referred

to as ‘TB stakeholders’). The present comprehensive international roadmap for TB research was prepared within this collaboration. It identifies knowledge gaps and describes key areas in which to encourage future investment, in order to enhance and harmonize funding across the research spectrum. The Roadmap will be reviewed regularly to ensure that it remains relevant as scientific advances are made and new tools and ideas emerge.



II. METHODS

1. Definition of TB research priorities

TB research priorities were defined by identifying strategic objectives and the activities required in fundamental research, development of new diagnostics, drugs and vaccines, and operational research. These strategic objectives and activities were established through:

- an inventory and systematic review of the research agendas of various groups and institutions over the past decade;
- a series of expert group meetings on each theme to identify gaps and priorities in all areas of TB research;
- broad consultations with TB stakeholders, including the relevant working groups of the Stop TB Partnership; and
- a systematic review of priority research

questions in recent reviews on new TB control tools.

An initial list of research priorities was prepared on the basis of those identified by the various expert group meetings, with active collaboration from a Core Group (including core members of the Stop TB Partnership Working Groups (WG) on New Diagnostics, New Drugs and New Vaccines, as well as the WGs on MDR-TB, TB/HIV and DOTS Expansion). This list was then compared with those identified in a thorough literature review, including previous TB research agendas, so as to select the most appropriate questions. The resulting list was then reviewed by an Expert Advisory Group with wide representation of multidisciplinary TB stakeholders. Both Groups are hereafter referred to as the 'technical working groups' (see composition in **Annex I**).

2. Preparation and structure of the document

There is currently no internationally agreed and recommended research classification system. In 2008, WHO proposed a framework for describing research priorities (6), covering five generic areas of activity:

- measuring the problem;
- understanding its cause(s);
- elaborating solutions;
- translating the solution(s) or evidence into policy, practice and products; and
- evaluating the effectiveness of solutions.

In accordance with this categorization, we outlined four general areas of TB research that cover the whole spectrum: (i) epidemiology (measuring the problem); (ii) basic or fundamental research (understanding its causes); (iii) research, development and evaluation of new tools, i.e. diagnostics, drugs and vaccines (elaborating solutions and evaluating the effectiveness of the solutions); and (iv) operational research (translating the solutions into practice, including better design

of health systems and preparation of algorithms with existing and new tools). Practically, as the epidemiological questions are interlinked with public health and operational research questions, we grouped them but decided to differentiate the control tools. The research questions were thus classified into five main categories:

- Fundamental research;
- Research and development of new diagnostics;
- Research and development of new drugs;
- Research and development of new vaccines; and
- Epidemiology, operational research and public health.

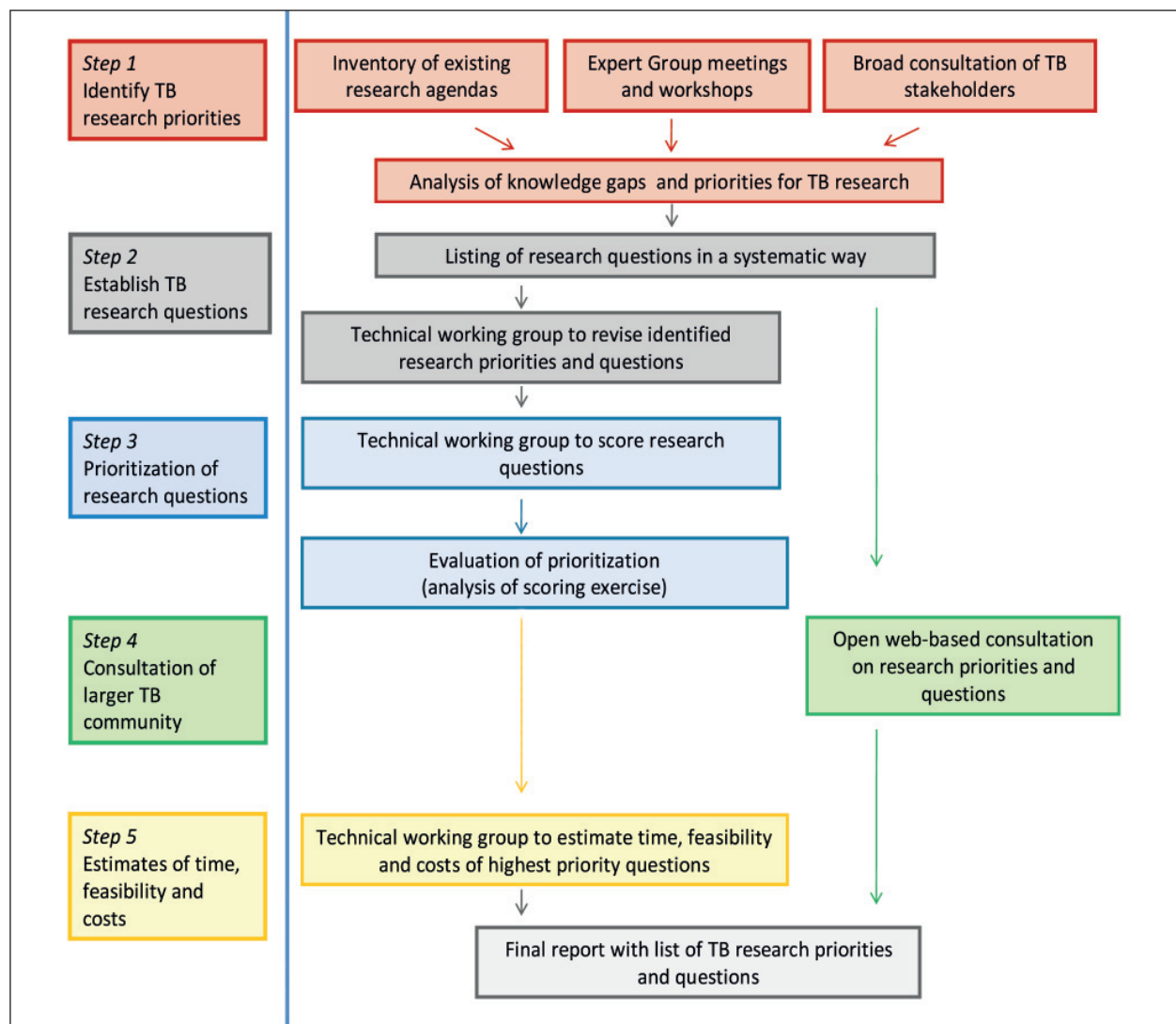
These research areas are defined in **Annex II**.

The detailed steps of the method used to identify and prioritize the research questions are described in **Figure 1**. A several-stage Delphi technique was used to prepare the initial list of research priorities. For each of the five areas, the main research

questions identified as priorities during the expert group meetings and workshops were listed together with the results of systematic reviews commissioned by the TB Research Movement and the review of published TB research agendas (July–September 2010) (see **Annex III**). The members of the Core Group and the Expert Advisory Group

were then asked to review and comment on the research priorities that had been identified in two successive occasions, with the possibility to add new research questions if appropriate (September–November 2010). Then, the two groups were asked to prioritize the research questions by the method described below.

FIGURE 1. Method used to identify and prioritize research questions (adapted from reference 7)



3. Method for prioritization

To score the research options independently and in a structured way, we chose to use a method for prioritization adapted from the Child Health Nutrition Research Initiative (2007) (7). Prioritization is based primarily on the value that a scientific question adds

to a research area, how critical it is for developing new tools, how it provides guidance in the use of new drugs, vaccines and diagnostics, and how it helps in preventing morbidity and mortality.

Between December 2010 and January 2011, members of the technical working groups were invited to score all the research questions for the following five criteria: effectiveness, necessity, deliverability, equitability and answerability. Prioritization of the research questions was based

on a grading scale in order to assess the importance of the question on the basis of the five criteria, as outlined in more detail in **Table 1**. The final prioritization scores were evaluated as described in **section 5** under.

TABLE 1. Definitions of the five criteria for prioritization

Criterion	Definition	Grading scale
Efficacy and effectiveness	Will answers to the research question provide knowledge, evidence and strategic directions for <i>reducing the disease burden</i> most effectively? ^a	No Probably not Probably Definitely
Necessity	Would answering the research question be ' <i>rate-limiting</i> ', i.e. would progress in the research area be slowed down until the answer to this particular question is found?	Yes No
	Would answering the research question be ' <i>rate-critical</i> ', i.e. would little or no progress be made unless the research question is answered?	Yes No
Deliverability	Will answers to the research question provide suitable data, knowledge, evidence and strategies for a deliverable output?	No Probably not Probably Definitely
Equitability	Will answers to the research question provide knowledge, evidence and strategies to reduce the disease burden equitably <i>in all population settings</i> , particularly in high-risk populations and populations in resource-poor settings? ^b	No Probably not Probably Definitely
Answerability	Will answers to the research question provide knowledge, evidence and strategies in an <i>ethical way</i> , i.e. protecting the rights of patients, avoiding harming them and maximizing their well-being?	No Probably not Probably Definitely

^a Including time and cost-effectiveness, as suitable

^b Including vulnerable populations such as children, HIV-infected people and prisoners

Each of the five sections (fundamental research; diagnostics; treatment; vaccines; epidemiology, public health and operational research) was evaluated separately. We used two methods to evaluate the results: a 'score proportions' analysis and a 'principal component' analysis. The details of

the methods used and the analyses carried out, as well as the criteria used to designate the 'highest', 'high' and 'medium' priorities are given in **Annex IV**. Overall, there was strong agreement between the results of the two evaluation methods; therefore, the results are given for the two methods together.

4. Open web-based consultation

In parallel with the prioritization of the research questions by the technical working groups, a web-based consultation was organized to involve the larger TB scientific community and everyone willing to participate in defining high-priority research questions. In contrast to the targeted consultation, the open consultation did not involve prioritization

of each research question; rather, participants were asked for feedback on the relevance of the research priorities and to comment on any aspects of the prioritization strategy. We received comments of high quality, all of which were considered in preparing this document.

5. Presentation of the document

In this document, we present the *convergence* of the score proportion and the principal component analyses with regard to the *highest* priorities (those identified as top priorities with both methods) and *high* priorities. Those questions that were graded as 'medium' in either of the two analyses are presented as *medium* priorities, in order to ensure complete, concise representation of research priorities and avoid the inherent bias due to use of one method over the other (and arbitrarily selecting one priority over another because it appears in one rather than the other analysis).

The results were then compared with the research priorities identified by the WHO/TDR Disease Reference Group on TB, Leprosy and Buruli Ulcer in similar areas (8). Overall, wide convergence of research priorities was found in the two reports, although the areas of research identified did vary in some cases. A few research priorities identified by the Disease Reference Group in the areas addressed by the present report were considered highly important; therefore, in discussion with the Group, we added them to the present document. These are clearly identified in the text (*'from the Disease Reference Group'*).

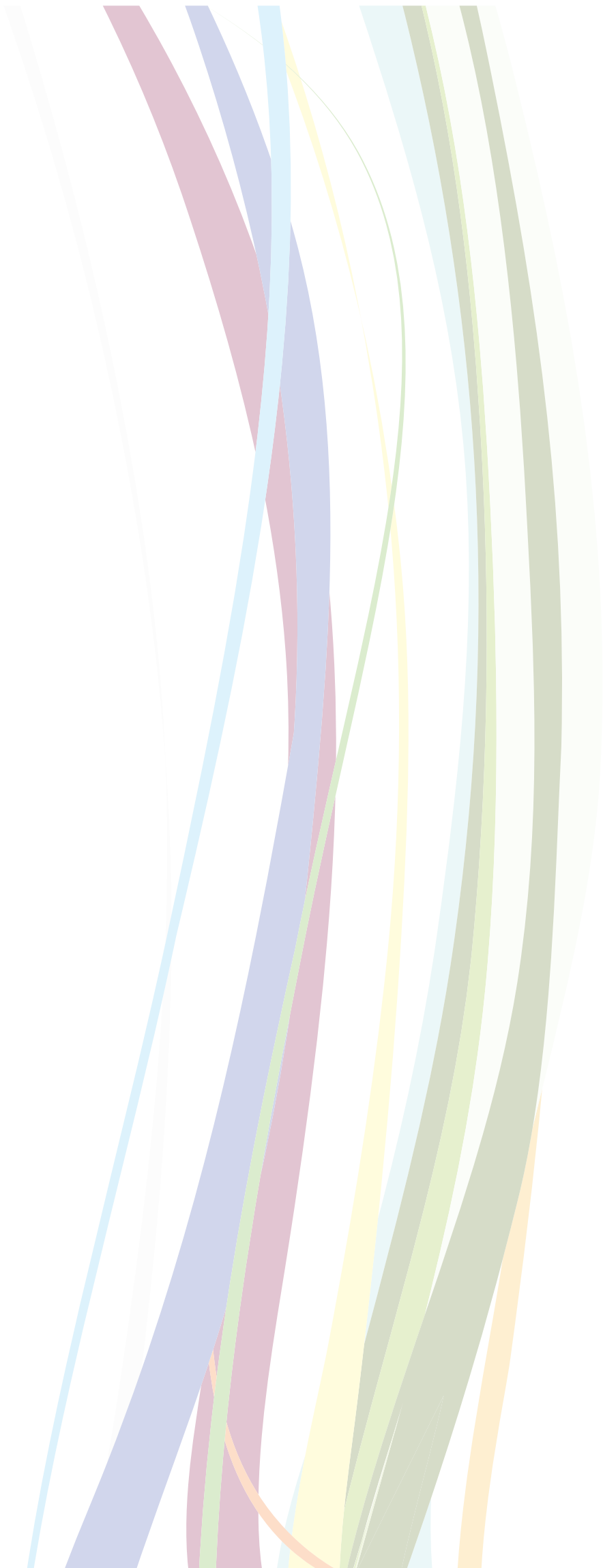
The last step in the evaluation was to estimate the *timeliness* and *feasibility* of the highest-priority questions. Members of the technical working groups were asked to categorize the highest-priority questions in each research area in terms of timeliness (as < 5 years, 6–10 years

or > 10 years) and feasibility (as moderate, good or excellent). The results are shown in tables for each research area.

During the process, epidemiological questions were being raised in each of the five main research areas. To illustrate the importance of epidemiology as a means of embracing the overall context ("setting the scene") and addressing local environmental aspects that should be addressed in TB control, an epidemiology section was created *post hoc*, assembling the epidemiological questions arising in each of the five research areas. Research priorities are therefore given for the following six research areas:

- Epidemiology,
- Fundamental research,
- Research and development of new diagnostics,
- Research and development of new drugs,
- Research and development of new vaccines,
- Operational and public health research.

Comments from the open web-based survey were also taken into account, especially regarding the presentation of questions. In some instances, additional research questions, found to be missing in the survey, were inserted. These are identified clearly as *'from the open web-based survey'*.



III. RESEARCH AREAS

1. EPIDEMIOLOGY

1.1 Background

A landmark in epidemiological research, which led to targeted interventions, is the control of TB in Alaskan Eskimos in the early 1950s (9); dramatic declines were brought about in TB incidence (by an unprecedented 13% per year) and mortality (by 30% per year) in this community. These declines were made possible by an increase in combined efforts for intensive case-finding, treatment, BCG vaccination of infants and preventive therapy. With the current tools for control of TB, similar combinations of activities will be needed to reduce the global TB incidence to below 1/1 000 000 by 2050 (5). Currently, global TB control efforts are focused on expanding DOTS in high-burden countries to achieve the target of curing 85% of all enrolled and treated patients. Despite current control efforts, however, and with a very slow decline in the estimated incidence of new TB cases since 2005, the absolute number of TB cases in the world is increasing. The most spectacular increases in TB rates since the 1980s have been seen in Africa, due to the concurrent epidemic of HIV, and in Eastern Europe in relation to the increase in drug-resistant TB. Two thirds of all TB cases are occurring in South-East Asia, where a slow, probably insignificant decrease in incidence is reported (7). Therefore, while much is known about the epidemiology of TB, our current approaches have failed to meet predictions.

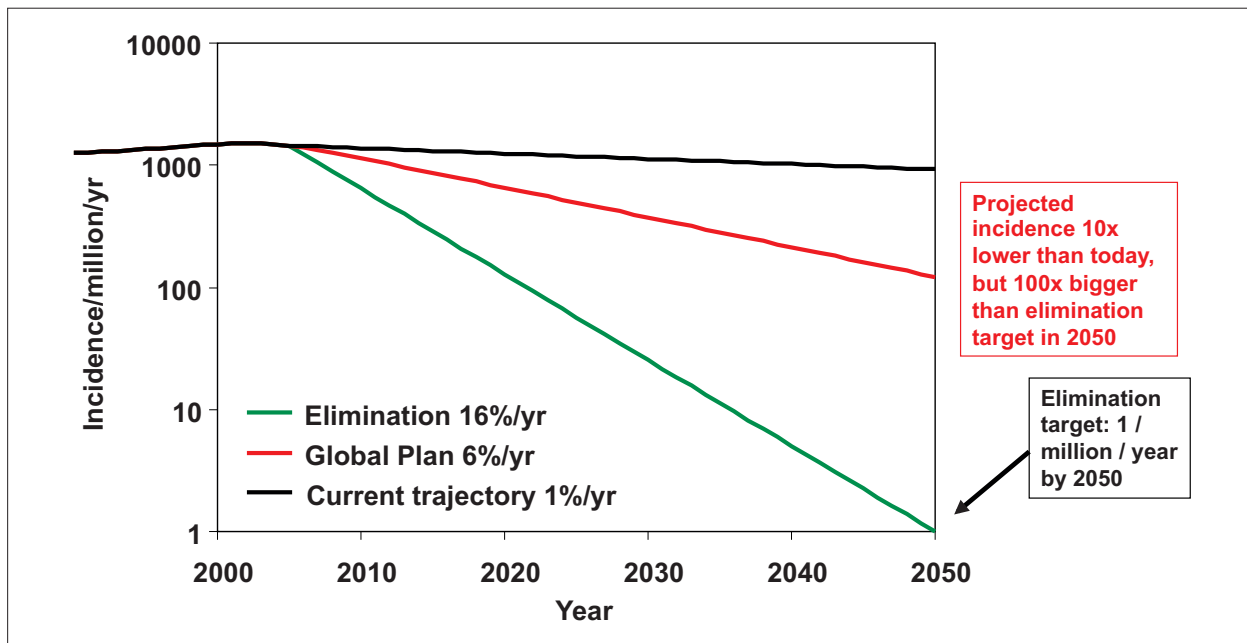
The main question is: “*Why can’t we achieve at global level the case reduction rates seen in the Alaskan Eskimo population?*” The answer is of course complex but most probably related to persistent transmission due to a combination of the following factors: (1) delayed diagnosis; (2) difficulty in accessing health care and initiating treatment; (3) ineffective prevention of infection progressing to disease; (4) different dynamics of transmission of various *M. tuberculosis* strains; (5) changing risk factors for TB; and (6) differences in economic factors, notwithstanding potential differences in the genetic make-up of populations (10). To eliminate TB by 2050, a rate of decline of about 16% per year would be needed, greater than that achieved in the Eskimo population under optimal conditions (Figure 2). We must combine interventions that improve the diagnosis of TB, prevent infection with a pre-exposure vaccine,

prevent active disease with preventive therapy and rapidly and effectively treat active disease, while at the same time reducing the risk factors for TB.

Ensuring appropriate TB control means that we must better understand the epidemiology of the disease and its transmission in populations and high-risk groups, in particular the precise mode of action and the contributions of the factors described above and the most effective targets they offer for intervention. Therefore, the burden of TB should be quantified in various populations and high-risk groups in endemic settings, and variations in the dynamics of TB in these populations and high-risk groups should be investigated. For this, it is important to define the smallest epidemiological unit that should be studied in order to capture the most relevant differences and thus address the respective contributions of host and pathogen and the effects of the environment on *M. tuberculosis* transmission. Greater collaboration with other scientific disciplines will contribute to understanding these epidemiological aspects, in order to identify the nature and contribution of specific risk factors and define the best courses for intervention.

Epidemiology is also necessary to assess the effect of control interventions at population level (the routine programme level), in order to identify targets for improving control activities. On a broader scale, this impact assessment identifies gaps in TB control, which should give rise to new interventions or adjustment of existing ones. In that sense, epidemiology could be viewed as closing the research cycle that leads from quantification of the burden of disease and its determinants at population level, to assessment of the effect of TB control interventions and identification of factors that are key to improving these interventions. For the latter, social and health system contexts must be understood so as to translate the findings of research into routine programme operations optimally. Lastly, social science and health systems research are crucial to maximizing the benefits of existing and new tools and are therefore essential components of research if the target of elimination is to be met.

FIGURE 2. Full implementation of the Global Plan to Stop TB 2006-2015: the 2015 MDG targets are reached but TB is not eliminated by 2050



1.2 Overall goal

To conduct epidemiological research that will improve knowledge of the distribution and natural history of TB, especially the roles of its various

determinants, so as to improve control activities, influence policy-making and ensure more efficient and effective methods of service delivery.

1.3 Major research areas and priority questions

The following areas and priority questions were identified to address the gaps that hamper effective TB control and contribute to better understanding of the epidemiology of TB.

High-priority questions:

1.3.1 Determine the burden of TB.

The importance of quantifying the burden of TB cannot be overstated. The prevalence, incidence and mortality from TB in general populations and in vulnerable populations must be accurately measured. This information is vital to TB programmes for planning purposes (e.g. quantification of drug requirements) and is needed for evaluating the effectiveness of control interventions.

- What is the burden of TB in various settings and high-risk areas, and what is the impact of DOTS implementation on the burden of disease?
- What are the best tools for measuring TB burden in limited-resources countries?
- What is the best programmatic model for surveillance in TB control in terms of epidemiology and management?
- What is the prevalence of latent tuberculosis infection in general populations and in high-risk groups (HIV-infected people, contacts of TB cases)? (*from the Disease Reference Group*¹)

¹ This question refers to the prevalence of infection, not the prevalence of some proxy of exposure, such as the results of a tuberculin skin test.

- What would be the probable epidemiological impact of widespread latent tuberculosis infection diagnosis and treatment on TB transmission in high-burden countries?

1.3.2 Understand variations in the dynamics of TB in different settings, and identify the social and biological drivers of *M. tuberculosis* transmission at population level.

High-priority questions:

- How can transmission of TB best be traced in households, health-care facilities and communities?
- How do the dynamics of TB vary in endemic settings and by how much? What is the size of the 'unit' we should study to capture the most relevant differences and to address the effect of the pathogen, the host and the environment on *M. tuberculosis* transmission?
- What are the relative contributions of the various foci of TB transmission (e.g. household, community, nosocomial transmission) at the population level, and what are the roles of the various demographic and social factors in specific settings?
- What is the potential contribution of molecular epidemiology to the identification of major foci of transmission?
- What is the reproductive fitness of strains with various drug resistance-conferring mutations? (*from the Disease Reference Group*)
- What are the social determinants of *M. tuberculosis* transmission in populations, what is their contribution to the risk of TB, and how could these be targeted in control programmes? (*from the Disease Reference Group*)
- What is the interaction between the pathogen, the host and social determinants on *M. tuberculosis* transmission in specific settings?
- What are the predictors of infectiousness of HIV-infected TB patients, particularly those with drug-resistant TB?

Key messages

- Epidemiological research is fundamental to understanding the causes and distribution of TB in populations, especially high-risk groups, and identification of the areas for targeted intervention.
- At the population level, the main priorities for research include:
 - sustained measurement of the burden of disease and of variations in the dynamics of TB according to the setting;
 - identification of the causes of low case detection and treatment, especially in certain high-risk groups and settings;
 - study of variations in the dynamics of TB according to setting and identification of the effect of the germ, the host and the environment on *M. tuberculosis* transmission;
 - the relative contributions of different foci of TB transmission (e.g. household, community, nosocomial transmission) at population level;
 - identification of the various biological, environmental, population-based and social drivers of *M. tuberculosis* transmission; and
 - further understanding of the interaction between the pathogen, the host and social determinants on *M. tuberculosis* transmission in specific settings and in high-risk populations (including TB-HIV coinfecting and MDR- and XDR-TB patients).

TABLE 2. Estimated timeframe and feasibility of answering the highest-priority questions in epidemiology.

	Timeframe (years)			Feasibility		
	<5	6 –10	>10	Moderate	Good	Excellent
What is the burden of TB in various settings and high-risk areas, and what is the impact of DOTS implementation on the burden of disease?	X				X	
What are the social determinants of <i>M. tuberculosis</i> transmission in populations, what is their contribution to the risk of TB, and how could these be targeted in control programmes? (from the Disease Reference Group)	X				X	
What are the predictors of infectiousness of HIV-infected TB patients, particularly those with drug-resistant TB?	X				X	
What is the best programmatic model for surveillance in TB control in terms of epidemiology and management?	X				X	
What are the best tools for measuring TB burden in limited-resources countries?	X				X	
What is the reproductive fitness of strains with various drug resistance-conferring mutations? (from the Disease Reference Group)	X			X		
What is the prevalence of latent tuberculosis infection in general populations and in high-risk groups (HIV-infected people, contacts of TB cases)? (from the Disease Reference Group)	X			X		
How can transmission of TB best be traced in households, health-care facilities and communities?		X			X	
What are the relative contributions of the various foci of TB transmission (e.g. household, community, nosocomial transmission) at the population level, and what are the roles of the various demographic and social factors in specific settings?		X			X	
How do the dynamics of TB vary in endemic settings and by how much? What is the size of the 'unit' we should study to capture the most relevant differences and to address the effect of the pathogen, the host and the environment on <i>M. tuberculosis</i> transmission?		X		X		
What is the interaction between the pathogen, the host and social determinants on <i>M. tuberculosis</i> transmission in specific settings?		X		X		
What would be the probable epidemiological impact of widespread latent tuberculosis infection diagnosis and treatment on TB transmission in high-burden countries?		X		X		

2. FUNDAMENTAL RESEARCH

2.1 Background

Although many studies have been conducted in humans and various animal models, our understanding of the natural history and pathological mechanisms of TB in humans remains incomplete. As stated by the Director of the United States National Institute for Allergies and Infectious Disease, Dr Anthony Fauci, “we need to better understand the delicate balance between the host and the pathogen in the context of the entire biological system”², and this requires a “radical and transformational approach”. Fundamental science is an integral part of a concerted, transformational research response to the global TB epidemic and is crucial for addressing critical questions in the development of new tools and strategies for prevention, diagnosis and cure. In this context, fundamental research will benefit from close collaboration among scientists in all the biomedical disciplines, including basic research, translational research, product development science, clinical research and epidemiology, in order to make significant, timely advances in the control of TB.

Many aspects of this agenda are already being addressed by scientists worldwide, and important data are emerging that can be integrated into the larger biomedical research roadmap to help understand the complex nature of TB and eliminate this disease by 2050. Fundamental science can improve knowledge and lead to new discoveries, which could ultimately result in the development of new, improved technologies. Engineering new technologies to identify, treat and prevent the disease requires solid knowledge about the pathogen that causes TB (*M. tuberculosis*) and the natural history and pathology of TB in humans. Sustained, adequate investment in fundamental science is essential to maintain the flow of new technologies into the product pipeline, and to ensure that a critical mass of new candidate products and strategies enter clinical development. Transforming the way we presently control TB requires innovative scientific approaches.

2.2 Overall goal

To address fundamental research questions that are key to the development of new diagnostics,

drugs and vaccines, to meet the goal of elimination of TB by 2050.

2.3 Major research priorities and questions

2.3.1 Characterize human TB by modern biomedical, clinical and epidemiological approaches.

Our understanding of the natural history of TB in humans is still incomplete. Better characterization of human TB will provide knowledge needed for subsequent research. Researchers in various scientific disciplines must work together to

understand the dynamics and life cycle of the pathogen, how humans respond to it, how and why disease develops, and how it eventually spreads to others. As TB is a chronic disease and does not develop in every infected person in the same way, it is critical to characterize carefully the steps that lead from exposure to disease and how both the host and the pathogen contribute to these steps.

² http://www.msnbc.msn.com/id/33890464/ns/health-infectious_diseases/ (accessed 27 January 2011).

Highest-priority question:

- What marks the transition between the key stages of human TB along the infection–disease spectrum, and what are the bacterial or host markers that indicate where an individual is placed along the spectrum and predict which individuals will progress from one phase of the spectrum to the next and why?

High-priority questions:

- What happens to *M. tuberculosis* metabolically and physiologically in the transition from infection to disease and during the evolution of granulomas into active cavities?
- Where are the bacteria located during the various phases of infection and disease, and is the location related to disease stage and disease outcome?
- Are there distinct bacterial subpopulations, and, if so, can we define bacterial subpopulations by (i) identifying lesion types that respond poorly to treatment, (ii) characterizing the microenvironments provided by different lesion types and (iii) characterizing the metabolic status of bacteria associated with different lesion types?

Medium-priority question:

- How do changes in host physiology due e.g. to other infections, nutritional status or diabetes influence TB disease progression?

2.3.2 Better understand the host–pathogen interaction.

M. tuberculosis causes TB, but it is not yet known precisely where the bacteria are located in the body and whether and how their location and numbers are responsible for the development of disease (11–15). Knowledge of mycobacterial pathogenesis is important for the design of more effective drugs that can reach all bacilli at whatever location in the human host and for developing better vaccines that induce efficient immunity to kill the bacteria, ideally at the time of initial infection. It is now understood that the genetic make-up of *M. tuberculosis* influences whether the body clears the infection, remains infected or develops active disease, but further studies into this complex host–pathogen relationship are needed (16). Of particular importance will be understanding why lung lesions in some patients

can control or ‘wall off’ bacteria and prevent disease, while the same lesions in others can break open and contribute to the growth and spread of bacteria from person to person (17). As not all aspects of the role and dynamics of these lesions can be studied in humans, animal models are needed for generating hypotheses that can be tested in humans. Additionally, novel imaging techniques could be used to study the course of individual lesions in humans.

Detailed understanding of the dynamic nature of TB during the host–pathogen interaction requires, first, definition of the respective contributions of the pathogen and the host, and then their interaction. It will be difficult to elucidate the complex, interlinked network of host–pathogen interactions with conventional microbiological or immunological experimental approaches. Therefore, an in depth understanding of the pathogenesis of *M. tuberculosis* and its cross-talk with the human host cell will require the application of a multi-scale systems biology approach.

With respect to the pathogen, it has been suggested that different populations of *M. tuberculosis* exist in humans during disease and that these populations differ in how they respond to drug treatment and immunity induced in the infected host. It remains to be confirmed in human patients whether these different populations exist, where they reside and to what extent they influence the timing and outcome of TB and reaction to treatment (12, 18).

With respect to the host, we must define how the immune system can restrain *M. tuberculosis* in most infected individuals and why this mechanism fails in others. It has been suggested that a combination of human and bacterial genetics, the size of the infectious dose, the location of bacteria in the infected host and the overall immune status all play a role.

How these factors contribute to the development of TB and how *M. tuberculosis* interacts with the immune system during progression from infection to disease is not yet fully understood (11, 17, 18). We must also understand how, in some people with documented prolonged exposure, the infection is prevented and they show no signs of stable infection (as measured with current tools).

Highest-priority questions:

- How does *M. tuberculosis* interact with the immune system during the various phases of progression from infection to disease?
- What components of the immune system and what components of the pathogen

are responsible for elimination of *M. tuberculosis* or for preventing reactivation of latent TB infection?

- Can an immune response to the pathogen or a vaccine prevent infection, i.e. block adherence to or invasion of *M. tuberculosis* in lung cells and tissues (mucosal immunity)?
- Why and how, in some individuals, does *M. tuberculosis* subvert the immune response, to induce a chronic inflammatory state with ineffective elimination of bacteria?
- Is persistence a natural occurrence in TB, or does it reflect the inability of current regimens to reach the persisting bacteria? Can we translate findings on persistence into drug targets to shorten treatment?

High-priority question:

- Is there a subpopulation who can resist TB infection in the absence of an antigen-specific immune response?

2.3.3 Use 'discovery science' to identify biomarkers that can better differentiate the various stages of the disease spectrum.

Answers to the questions listed above will contribute to the identification of biomarkers that

will be useful in the development of new candidate diagnostics, drugs and vaccines. Understanding the stage of the disease at which individuals are across the spectrum is key to designing tools for health care intervention. For instance, in order to identify people who are infected with *M. tuberculosis* but who have not yet developed disease, either components of the *M. tuberculosis* complex or characteristics of the host immune response must be identified that clearly indicate the presence of live *M. tuberculosis*, irrespective of where the bacilli are harboured in the body and whether the person's immune system is healthy or compromised (19, 21).

Highest-priority question:

- Which biomarker or combinations of biomarkers will help distinguish the various stages of the spectrum of TB infection (from sterilizing immunity to active disease) and will allow accurate identification of patients at each level, including detection of latently infected people who are at highest risk for progression to disease? Which specific platform and which human samples (e.g. sputum, blood or urine) will be most useful?

Key messages

- Understanding the stages of TB disease progression and identifying markers of progression are key to the generation of knowledge necessary for developing new tools and strategies for better TB control.
- Better characterization of human TB is required for subsequent research. The highest priority is to better understand the transitions between the stages of human TB, from infection to disease, and the bacterial or host markers that indicate the stage of disease and predict which individuals will progress from one phase to the next.
- Highest priority is given to better understanding of the host–pathogen interaction, particularly:
 - the interaction of *M. tuberculosis* with the immune system during the phases of progression from infection to disease,
 - the mechanisms leading to persistence or elimination of bacilli in various conditions (e.g. according to age or HIV infection),
 - the identification of the respective components of the host's immune system and of the pathogen that are responsible for elimination of *M. tuberculosis* or for preventing reactivation of latent TB infection and
 - the role of mucosal lung immunity in addition to systemic immunity.
- Great importance is given to identification of biomarkers (or combinations of biomarkers) that will help distinguish the stages of TB and will allow accurate identification of patients at various levels of the spectrum (including the detection of latently infected individuals, who are at highest risk for progression to disease).

TABLE 3. Estimated timeframe and feasibility of answering the highest-priority questions in fundamental science

	Timeframe (years)			Feasibility		
	<5	6 -10	>10	Moderate	Good	Excellent
	What marks the transition between the key stages of human TB along the infection-disease spectrum, and what are the bacterial or host markers that indicate where an individual is placed along the spectrum and predict which individuals will progress from one phase of the spectrum to the next and why?		X			X
How does <i>M. tuberculosis</i> interact with the immune system during the various phases of progression from infection to disease?		X			X	
Can an immune response to the pathogen or a vaccine prevent infection, i.e. block adherence to or invasion of <i>M. tuberculosis</i> in lung cells and tissues (mucosal immunity)?	animal & case-contact studies	vaccine studies			X	
Is persistence a natural occurrence in TB, or does it reflect the inability of current regimens to reach the persisting bacteria? Can we translate findings on persistence into drug targets to shorten treatment?		X		human studies	mouse studies	
Which biomarker or combinations of biomarkers will help distinguish the various stages of the spectrum of TB infection (from sterilizing immunity to active disease) and will allow accurate identification of patients at each level, including detection of latently infected people who are at highest risk for progression to disease? Which specific platform and which human samples (e.g. sputum, blood or urine) will be most useful?		X			X	
What components of the immune system and what components of the pathogen are responsible for elimination of <i>M. tuberculosis</i> or for preventing reactivation of latent TB infection?		X		X		
Why and how, in some individuals, does <i>M. tuberculosis</i> subvert the immune response, to induce a chronic inflammatory state with ineffective elimination of bacteria?		X		X		

3. DIAGNOSTICS

3.1 Background

Although microscopic examination of sputum is poorly sensitive for detecting TB bacilli, it remains the only widely available diagnostic tool for identifying TB in most high-burden countries (22). By the time TB is diagnosed from sputum smears, transmission has generally already occurred, resulting in new TB cases (16). Drug susceptibility testing, if available, is usually performed only after treatment failure, delaying the diagnosis of drug resistance and removing many opportunities to interrupt transmission. While TB treatment success rates have been steadily improving, TB case detection remains markedly less than optimal: WHO estimated that globally it was only 63% in 2009 (23). The lack of effective quality-controlled diagnostic tools jeopardizes potential gains in TB control.

Substantial progress has been made in research and development on new diagnostic tools, and many promising new techniques have been developed recently (19), including liquid culture for rapid drug susceptibility testing, combined with rapid speciation methods, which was endorsed by WHO in 2007. The molecular line probe assay for rapid screening for multidrug resistance was endorsed in 2008 and is being used in an increasing number of countries. Non-commercial culture methods for rapid drug susceptibility testing were endorsed by WHO in 2009. More sensitive definitions of ‘positive smear’ and ‘smear-positive case’ and a reduced number of smear examinations required for microscopy were recommended by the WHO in 2007. This approach, coupled with recommended use of light-emitting diode fluorescence microscopy for more sensitive smear microscopy (endorsed in 2009) and use of same-day sputum collection and examination to reduce initial default (called

‘front-loaded’ microscopy, also endorsed in 2009), significantly increases the likelihood of better case detection at the most peripheral levels of health systems. Most recently, a newly developed, fully automated, cartridge-based nucleic acid amplification assay, Xpert MTB/RIF, to detect drug-susceptible and rifampicin-resistant TB in less than 2 hours, was endorsed by WHO (2010) and is now being introduced and adapted on a wide scale in health services (24).

Despite this progress, candidate tools to detect active TB at the point of care, predict disease progression and screen for MDR-TB and XDR-TB, as well as HIV-associated TB and paediatric TB, are still lacking (19). Moreover, while much progress has been made in developing and introducing new diagnostic tools, some new technologies require elaborate and expensive biosafety infrastructure, limiting their use to district facilities and national reference laboratories. Also, the availability of new diagnostic tools does not necessarily ensure their wide adoption and use; translation of policy into practice requires better understanding of the barriers to implementation and tested approaches to overcoming such barriers, so as to develop strategies to improve patients’ access to existing and new technologies (19, 25). Accurate detection of all forms of TB for appropriate treatment and detection of latent TB infection for active disease prevention are essential components of the elimination campaign. For all these reasons, diagnostic research is needed across the research spectrum—from discovery to demonstration and impact evaluation—to ensure that appropriate, affordable diagnostic tools are available at all levels of health care.

3.2 Overall goal

To increase TB case detection with new and improved diagnostics to detect active disease at the point of care, diagnose latent TB infection,

predict disease progression, and rapidly screen and diagnose MDR- and XDR-TB, HIV-associated TB and paediatric TB.

3.3 Major research areas and questions

3.3.1 Evaluate biomarkers identified in fundamental studies for use as diagnostic tools.

The development of a rapid, accurate point-of-care test requires identification of biomarkers that can be incorporated into highly sensitive platforms that are simple to use and affordable and can be used in health clinics, thereby reducing diagnostic delay. To address this long-term goal, a series of priority questions must be addressed.

Highest-priority question:

- Can fundamental studies identify bacterial and/or host molecules (or multi-molecular signatures) that differentiate between people with active TB disease, those with latent TB infection and those not affected by TB that can be detected by a point-of-care test?

High-priority questions:

- Can we compile a systemic marker of bacterial load in TB patients by (i) detecting bacterial components in specimens such as blood, urine or breath, (ii) measuring bacteria-specific metabolic reactions or (iii) host markers that are quantitatively related to antigen concentration?
- Which novel TB-specific antigens or antibodies could be used for the development of an accurate point-of-care diagnostic test conducted with an existing point-of-care platform (e.g. immunochromatographic assays used for malaria and HIV)?

3.3.2 Design and validate a set of tools for diagnosis of active drug-sensitive TB, drug-resistant TB and latent TB infection that are feasible and applicable at various health-care levels in high-burden settings.

Despite an unprecedented level of interest and activity in developing new tools for TB diagnosis, new, affordable, simple diagnostic tools are still required to diagnose active TB accurately and rapidly in all settings, from hospitals to

communities. Detection of latent TB infection for active disease prevention will be a key component of the elimination campaign. Therefore, a number of key questions should be addressed.

Highest-priority question:

- How can novel tools for diagnosis, such as measurement of metabolites, RNA, lipids in sputum, urine and/or blood, and volatile compounds in breath, be simplified and validated for use as point-of-care diagnostics in high-burden settings?

High-priority questions:

- What are the most efficient, rapid, multifunctional diagnostic platforms that might allow testing for TB disease and/or simultaneous or sequential testing of TB and HIV infection and other infectious diseases, particularly in smear-negative patients (HIV-infected people, children)?
- How could the platforms for currently used diagnostic markers be advanced and simplified (e.g. visualization or nucleic acid amplification test detection in sputum) to use them as point-of-care tests in high-burden settings?

3.3.3 Improve existing diagnostic tests for active drug-sensitive and drug-resistant TB and latent TB infection at various health-care levels in various groups in high-burden settings.

Current diagnostic procedures have severe limitations. Sputum microscopy detects only a proportion of all TB cases; smear-negative TB, extrapulmonary TB, childhood TB, HIV-associated TB and drug-resistant TB are diagnostic challenges, and the available tests perform poorly in these cases. Culture of mycobacteria on specific solid media is the gold standard for bacteriological confirmation of the disease, but it requires a suitable laboratory infrastructure that is not available in peripheral laboratories and 6–8 weeks to show positivity, delaying treatment, especially of patients for whom smear

microscopy has limitations. Assessment of drug susceptibility by culture on solid media is slow, tedious and difficult to perform under field conditions. For these reasons, newer algorithms and tests are needed, to shorten the time required for establishing diagnosis of all forms of TB, improving patient-relevant outcomes and reducing transmission of TB.

Highest-priority question:

- How can the existing diagnostic tests be most efficiently combined to optimize detection of drug-sensitive and drug-resistant TB in different population settings (children, people living with HIV) and at all health-care levels so as to minimize morbidity, mortality and transmission of TB?

High-priority question:

- In children, which combinations of methods for collecting specimens for smear microscopy (e.g. nasopharyngeal aspirate, induced sputum or throat swab) can replace gastric aspirates, while providing the same yield of specimens collected in the same time and requiring similar skills?

3.3.4 Evaluate new diagnostic tools and conduct demonstration studies, followed by evaluation of the programmatic impact of all diagnostic tools.³

The availability of new diagnostic tools does not necessarily ensure their adoption and implementation. Translation of research findings into policy and subsequently into practice requires better understanding of the barriers to implementation and methods to overcome such barriers. Operational research on different ways of using current and new diagnostics in national TB programmes in high-burden settings is required.

3.3.4.1 Conduct validation and operationalisation studies for new nucleic acid amplification tests for diagnosis of various forms of TB in resource-limited settings.

Highest-priority questions:

- What are the feasibility, impact and cost-effectiveness of automated, cartridge-based nucleic acid amplification tests if used at the point of care?
- What will be the role of simplified nucleic acid amplification tests in the diagnosis of TB in resource-limited settings, and what are the implications for replacement of smear microscopy? What is their performance in high HIV prevalence settings, in the diagnosis of active TB in children of various ages and in the diagnosis of extrapulmonary TB?

3.3.4.2 Evaluate new diagnostic tools.

Highest-priority questions:

- How does the new test perform in terms of feasibility (changes in laboratory structure, biosafety, storage and logistics), and reduction of the diagnostic delay and laboratory technician workload in the setting(s) and population(s) in which the test is clinically indicated?
- Does the test increase the number of patients who are treated and cured, and does it improve the outcomes of patients with suspected TB who are referred for diagnosis and evaluation?
- What does 'impact' mean? What important outcomes with respect to patients, populations, health systems and epidemiology should be measured to assess the impact of improved diagnostic products? Which preliminary data are required to allow analysis and prediction of the impact?

³ Including studies on the diagnosis of active TB and latent TB infection, HIV-TB coinfection and drug-resistant TB in high-burden countries

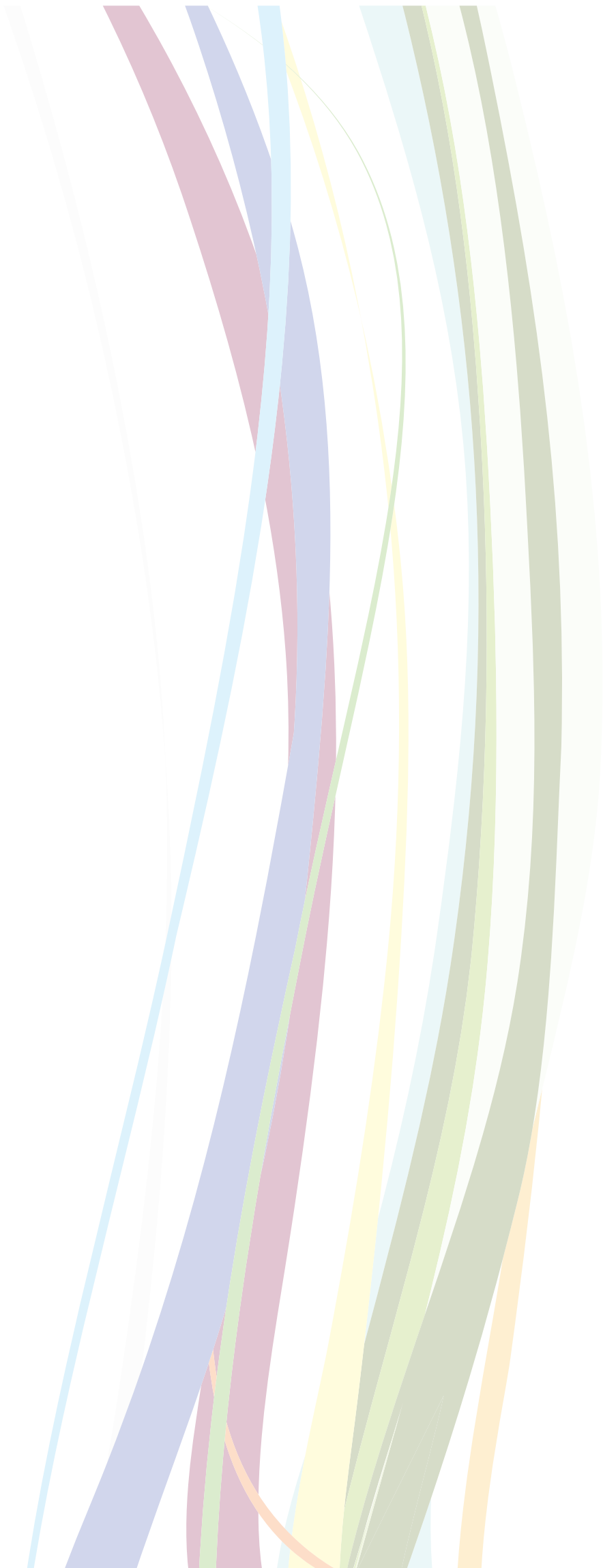
- What programmatic impact does the introduction of novel diagnostic tools or a combination of existing and novel diagnostic tools have on the detection of smear-negative TB (implementation, feasibility, equitable access by all patients, cost-effectiveness, patient outcomes and diagnostic delay in routine settings)?
 - What are the cost-effectiveness, the human resource implications, the outcomes of patients with suspected TB and the benefits to patients (including improved cure rates, proportion of patients completing therapy and reduction in treatment failure) of introducing the novel diagnostic test or combination of tests?
- High-priority questions:*
- What are the accuracy and reproducibility of new diagnostic assays in the diagnosis of active TB (including extrapulmonary TB), and latent TB infection in specific populations (e.g. children, HIV-infected people, people on immunosuppressive therapy and other conditions resulting in immunocompromise such as diabetes, cancer, renal failure, organ transplantation)?
 - What is the effect of the test on clinical decision-making? Does the new diagnostic test lead to changes in TB diagnosis (change in diagnostic thinking)?

Key messages

- The highest-priority topics are:
 - (i) identification of bacterial and/or host molecules that differentiate people at different stages of the disease spectrum (including predictive markers of progression from latent tuberculosis infection to active TB), and
 - (ii) simplification and validation of novel tools for diagnosis at the point of care.
- A high priority is studying how to combine existing and new diagnostics to optimize the detection of various forms of TB (including drug-sensitive, drug-resistant and latent TB infection) in various population settings and at all health-care levels.
- Of great importance are definition and evaluation of the performance of new diagnostic tests in terms of feasibility, cost-effectiveness, reduced diagnostic delay and impact on clinical decision-making and patient benefit.
- Particular reference is made to the need to identify combinations of methods for collecting useful specimens from children.
- Another high priority is development of a systemic marker of bacterial load in TB with various samples and methods.
- The automated nucleic acid amplification test is potentially revolutionary for TB control, but it must be decentralized to points of treatment, and its use would have to be scaled up rapidly in order to achieve an impact at population level, particularly in resource-limited settings.

TABLE 4. Estimated timeframe and feasibility of highest-priority questions in TB diagnostics.

	Timeframe (years)			Feasibility		
	< 5	6 - 10	>10	Moderate	Good	Excellent
How can the existing diagnostic tests be most efficiently combined to optimize detection of drug-sensitive and drug-resistant TB in different population settings (children, people living with HIV) and at all health-care levels so as to minimize morbidity, mortality and transmission of TB?	X					X
What are the feasibility, impact and cost-effectiveness of automated, cartridge-based nucleic acid amplification tests if used at the point of care?	X					X
What will be the role of simplified nucleic acid amplification tests in the diagnosis of TB in resource-limited settings, and what are the implications for replacement of smear microscopy? What is their performance in high HIV prevalence settings, in the diagnosis of active TB in children of various ages and in the diagnosis of extrapulmonary TB?	X					X
How does the new test perform in terms of feasibility (changes in laboratory structure, biosafety, storage and logistics), and reduction of the diagnostic delay and laboratory technician workload in the setting(s) and population(s) in which the test is clinically indicated?	X					X
Does the test increase the number of patients who are treated and cured, and does it improve the outcomes of patients with suspected TB who are referred for diagnosis and evaluation?	X					X
What programmatic impact does the introduction of novel diagnostic tools or a combination of existing and novel diagnostic tools have on the detection of smear-negative TB (implementation, feasibility, equitable access by all patients, cost-effectiveness, patient outcomes and diagnostic delay in routine settings)?	X					X
What are the cost-effectiveness, the human resource implications, the outcomes of patients with suspected TB and the benefits to patients (including improved cure rates, proportion of patients completing therapy and reduction in treatment failure) of introducing the novel diagnostic test or combination of tests?	X					X
What does 'impact' mean? What important outcomes with respect to patients, populations, health systems and epidemiology should be measured to assess the impact of improved diagnostic products? Which preliminary data are required to allow analysis and prediction of the impact?	X	X				X
Can fundamental studies identify bacterial and/or host molecules (or multi-molecular signatures) that differentiate between people with active TB disease, those with latent TB infection and those not affected by TB that can be detected by a point-of-care test?		X			X	
How can novel tools for diagnosis, such as measurement of metabolites, RNA, lipids in sputum, urine and/or blood, and volatile compounds in breath, be simplified and validated for use as point-of-care diagnostics in high-burden settings?		X			X	



4. TREATMENT

4.1 Background

Although the current 6-month treatment regimen for drug-susceptible TB was a tremendous advance over the historic 18-month treatment and has been proven to be highly efficacious, it is still inadequate in many aspects: it is still lengthy, ineffective against resistant forms of TB and interacts with commonly used ART (26). The regimens currently used for treatment of MDR- and XDR-TB are long, toxic, poorly tolerated, expensive and of limited efficacy (26, 27). Substantial progress in drug development was made in the past decade, with new or repurposed compounds progressing through clinical development (28). These compounds could become an important part of future regimens that will contribute to the global effort to control TB.

There are still many challenges to be overcome to produce better TB therapy. A shorter regimen that is safe, well tolerated, effective against drug-susceptible and drug-resistant TB, child-friendly and ART-compatible is urgently needed (26, 29, 30). This will require a new generation of more effective

drugs and approaches to accelerate their evaluation and introduction. Keeping the ‘drug pipeline’ filled is essential for further progress in TB treatment. The most pressing needs are for highly effective and short-duration drug combinations, identification of biomarkers of treatment response and sterilizing cure, studies in paediatric populations, new clinical trial designs, greater trial capacity and optimized clinical management of TB–HIV coinfection. Additionally, better understanding of the relation between active and latently persisting tubercle bacilli would help shorten and improve current treatment of latent tuberculosis infection, especially in children and HIV-infected individuals (17).

Further down the scale, all new and repurposed compounds must be tested under appropriate conditions. In order to ensure that large-scale multicentre clinical trials can be carried out under international requirements, parallel efforts should be undertaken to build capacity and develop appropriate infrastructures in several endemic countries.

4.2 Overall goal

To develop shorter TB regimens to cure all forms of TB that are safe, compatible with ART, suitable for children, effective against latent tuberculosis

infection, affordable, easily managed in the field and that remain effective by limiting the development of drug resistance.

4.3 Major research priorities and questions

4.3.1 Develop new drugs and treatment strategies.

The life cycle of *M. tuberculosis* in patients must be better understood. For this, studies and data should be derived from all areas of microbial science—from genetics to nutrient use to how the bacterium builds its cellular components—so that the life cycle of the pathogen can be reassembled and integrated into a common strategy, termed ‘systems biology’ (30).

This comprehensive view could make it possible to identify points of vulnerability of the pathogen to which drugs could be directed, which might not have been identified with existing methods. Understanding the mechanisms of action of current anti-TB drugs would add important knowledge. In addition, understanding the mechanism of genetic mutations that cause resistance to second-line drugs would help in preventing and diagnosing this condition.

Highest-priority questions:

- What are the contributions and mechanisms of action of currently used anti-TB drugs and of agents in development or in clinical trials against *M. tuberculosis*, and how can these be combined to improve treatment efficacy?
- Which bacterial gene mutations predict resistance to second-line drugs, and what is the clinical importance of mono-resistance and cross-resistance between second-line drugs measured in vitro?
- Can we facilitate modern cell- and target-based drug discovery by (i) developing systems biology models of mycobacterial metabolism and physiology; and (ii) identifying a quantitative, reproducible, accurate, experimentally tractable, operational definition of bacterial death?⁴

High-priority question:

- Can we design predictive models for synergistic and antagonistic effects of drug combinations?

Additional question (from the web-based survey):

- How can we ensure that a substantial proportion of all chemical entities ever synthesized are screened in cell-based assays for antimycobacterial activity?⁵

4.3.2 Develop a shorter regimen for drug-susceptible TB that can be used in combination with HIV treatment.

As treatment of TB is based on combinations of drugs, it is essential to start investigating the safety and efficacy of new regimens, including new or repurposed drugs, early enough in their clinical development to speed up introduction of new drug regimens. Preclinical and early clinical data on novel drugs help to determine whether they are safe and effective in humans. Early bactericidal activity studies of single drugs and combinations, in association with phase II sputum microbiology studies, will advance potential drug combinations to further clinical development phases. In parallel, studies of interactions between new TB drugs and

antiretroviral agents must also be started early in the drug development pathway. Therefore, it is a high priority to address both optimization of existing first-line anti-TB drugs and introduction of novel TB drugs and drug regimens, as well as methods for early identification of optimal combination of drugs and of optimal dosages and durations of treatment in various populations. Furthermore, research is needed to identify markers of treatment efficacy that could shorten the duration of trials.

Highest-priority questions:

- What are the optimal dosage, safety and efficacy of novel TB drugs (in all populations, including children and HIV-infected people)? How can existing and novel TB drugs be optimally combined into safe, well-tolerated multidrug regimens that minimize drug–drug interactions and ensure an effective (i.e. relapse-free) cure?
- What is the optimal length of novel TB treatments for all populations, and the optimal time to start treatment in HIV-infected patients?
- What are the optimal length and dosage of rifamycin-based TB treatment in children and in people living with HIV? Are the currently recommended doses too low? How can the sterilizing activity be maximized, and what would be the effect of higher dosages on safety, toxicity and interactions with other TB drugs or ART?
- Which biomarkers or combination of markers will help to measure the treatment effect that correlates with bactericidal and sterilizing activities of tested drugs, in order to allow shortening of clinical trials?

High-priority question:

- How can drug combinations that include new drugs be optimally tested early enough in overall drug development? What model of drug testing should be used to investigate drug combination regimens (including fixed-dose combinations) and drug–drug interactions early in the drug development plan?

⁴ The interaction of chemical and biological research is also key to answering these questions.

⁵ The number of compounds that are active against potential targets would increase tremendously, and the number of potential drugs as well. This is by far the most efficient way to identify new drug candidates.

4.3.3 Develop a safer, more efficacious, shorter regimen for drug-resistant TB that is compatible with HIV treatment.

New drugs, especially those with novel mechanisms of action, can form the core of shortened regimens for the treatment of drug-resistant TB. While new drug candidates are being tested in superiority trials in patients with MDR-TB, phase II trials of drug combinations should be carried out early in order to identify suitable combinations of drugs that offer significant advantages over the present regimen and that should be advanced for testing in phase III trials. Large-scale trials should be conducted at several sites in areas with a high burden of MDR-TB to ensure sufficient, timely enrolment. Determination of appropriate combination regimens also requires pharmacokinetics and drug–drug interaction studies. The highest-priority questions address the introduction of novel drugs against drug-resistant TB and their combination with existing drugs in shorter, safer regimens. Additional high-priority questions address identification of the optimal combination of drugs for both treatment of drug-resistant TB and prevention of TB in contacts of MDR-TB cases.

Highest-priority questions:

- What are the optimal dosage, safety and efficacy of novel drugs against drug-resistant TB? How can existing and novel drugs against drug-resistant TB be optimally combined to minimize drug–drug interactions and to ensure an efficacious (i.e. relapse-free), safe, well-tolerated multidrug regimen?
- What is the optimal duration of combined treatment containing newly introduced drugs against drug-resistant TB?

High-priority questions:

- What are the best methods for defining the optimal combination (bactericidal and sterilizing activities of combinations) of existing and novel drugs for shortening treatment of MDR- and XDR-TB?
- What are the optimal drug combinations in terms of tolerability, efficacy, safety and adherence for contacts of patients with MDR-TB, including children and HIV-infected people?
- How effective is the standard WHO re-treatment regimen; does it amplify drug resistance, and, if so, for which baseline resistance pattern(s)?

Medium-priority questions:

- What are the optimal dose, safety and clinical efficacy of different standard and individual MDR-TB regimens (individual drug effect, number and combination of second-line drugs) in different settings with different drug resistance patterns?
- What are the value, efficacy and risks of preventive therapy for contacts of patients with drug-resistant forms of TB, including children?

4.3.4 Develop safe, reliable, user-friendly drug regimens suitable for all forms of TB in children and compatible with HIV treatment.

All drugs that are used in adults should also be tested in children. Because children frequently metabolize drugs differently from adults, pharmacokinetics studies are required to determine the distribution of drugs and formulations in children, to ensure that treatment can be fully adapted to them and, if possible, made available in fixed-dose combination formulations. Drug–drug interaction studies with current first- and second-line TB drugs, as well as potential new drugs and ART, are also necessary.

Highest-priority questions:

- How can we ensure optimal treatment duration and dosage of all TB drugs in children of all ages (including those < 2 years and infants < 3 months), whether they are HIV infected or not, taking into account differences in absorption, distribution and excretion of pharmacological agents in children?
- What are the key drug–drug interactions of existing and new TB drugs in HIV-infected and -uninfected children of different ages? What are the effects of malnutrition and co-administered antiretroviral agents?

Medium-priority question:

- What aspects of the design and conduct of clinical trials (e.g. choice of end-points, gold standard, sample size, inclusion criteria and clinical definitions) are specific to children, and at what point in drug development should studies be undertaken in children?

4.3.5 Develop safer, more effective, shorter regimens for TB–HIV coinfecting patients.

TB–HIV coinfection is a major challenge for TB control, as HIV infection significantly increases the risk for active TB. Severe drug–drug interactions can occur between rifamycin-containing first-line TB therapy and antiretroviral agents, as compounds in the rifamycin class are strong inducers of cytochrome P450 enzymes, or due to diverse drug efflux mechanisms and other enzyme systems. In addition, coinfecting patients are at increased risk for immune reconstitution inflammatory syndrome, and HIV infection is associated with a higher risk for adverse events. Treatment of coinfecting patients taking protease inhibitor-based regimens is more complicated. Rifabutin, an alternative rifamycin, has less effect on protease inhibitor concentrations, but a safe, effective, standardized dosing approach for the combination has not yet been defined, and suitable paediatric formulations are not available. New TB drugs without drug–drug interactions with protease inhibitor-based therapy are needed for effective treatment of the TB–HIV coinfecting population. Therefore, drug–drug interaction studies with current first- and second-line TB drugs and also with potential new TB and antiretroviral drugs are necessary.

High-priority questions:

- What is the optimal timing of initiation of ART in HIV-infected people with active TB to prevent the immune reconstitution inflammatory syndrome while still providing optimal, life-saving ART?
- What is the interaction between existing second-line TB drugs and antiretroviral drugs, and how can adverse events be best recognized and managed?
- What are the safety, efficacy and optimal dosage of rifabutin? What are its drug interactions in TB treatment? How can we best prevent acquired rifamycin-resistant failure in HIV-infected people receiving ART?

Medium-priority question:

- What are the best combined-treatment strategies for TB and HIV in different populations (including high-risk populations such as pregnant women, women of childbearing age, people with liver disease

and injecting drug users) that would minimize drug–drug interactions between TB and antiretroviral drugs and overlapping toxicity (including dosing and duration of therapy)?

4.3.6 Develop safer, shorter, highly effective regimens for drug-susceptible and drug-resistant latent TB infection that are compatible with HIV treatment and suitable for children.

The central target for TB control is reducing person-to-person disease transmission by early, effective treatment of infectious TB. An additional target is to prevent active TB in people infected with *M. tuberculosis* and who have a high risk for progression, such as children and people living with HIV. Clinical guidelines currently recommend the preventive use of isoniazid for at least 6 months, although this presents a number of practical and operational challenges, especially in high-burden countries. Clinical trials are needed to evaluate the safety and efficacy of novel drugs or drug regimens for the prevention of active TB among people with latent infection.

Highest-priority question:

- What is the optimal TB preventive therapy in terms of efficacy, safety, tolerability and duration of protection that can be used in HIV-infected adults and children, particularly those receiving ART?

High-priority questions:

- Can novel drugs rapidly kill latent or persisting bacilli in people with latent TB infection? If so, how should they be optimally combined to introduce a safer, shorter, more efficacious preventive drug regimen for adults and children (including HIV-infected people and patients receiving ART)?
- What are the optimal time for initiation and the best administration schedules of preventive TB therapy in HIV-infected patients receiving ART or not (i.e. repeated courses or lifelong preventive therapy), especially pregnant and breastfeeding women and children?

Medium-priority question:

- What are the efficacy, cost-effectiveness, optimum duration and potential long-term adverse events of current treatment regimens for latent TB infection in adults, children, HIV-infected patients and other special populations (such as pregnant women and people with underlying liver disease such as hepatitis B or C)?

Key messages

- Prominent fundamental research topics must be addressed that will result in the development of new drugs. These include:
 - (i) design of systems biology models of *M. tuberculosis* metabolism and physiology to facilitate modern cell- and target-based drug discovery;
 - (ii) identification of the mechanisms of action of currently used anti-TB drugs or drugs presently in development or in clinical trials; and
 - (iii) further understanding of the persistence of bacilli for the identification of drug targets.
- The highest-priority topics in drug development for TB are related to:
 - development of new TB drugs (identification of optimal dosage, safety and efficacy) and their interaction with other (TB and non-TB) drugs, and
 - identification of optimal treatment regimens as early as possible in overall drug development, for all populations (patients with drug-sensitive and drug-resistant TB, TB–HIV coinfection and children).
- The same high-priority questions apply to TB preventive therapy (optimal dosage, safety, efficacy of novel TB drugs and their combination and optimal duration of treatment), for both HIV-infected people and contacts of TB cases.
- Questions on the interaction between first- and second-line drugs and antiretroviral agents and the search for new anti-TB drugs that are fully compatible with ART for the treatment of HIV–TB coinfection are also of high priority. These questions are also valid for children, especially those suffering from an intercurrent affection (such as malnutrition).
- Identification of the best methods to test and identify optimal combinations of drugs early enough in overall drug development and identification of best models of drug testing to investigate drug combination regimens (including fixed-dose combinations) and drug–drug interactions early in the drug development plan are high priorities.
- Determination of biomarkers or combinations of biomarkers of disease activity would allow early evaluation of bactericidal and sterilizing activities of drugs so as to shorten clinical trial duration.

TABLE 5. Estimated timeframe and feasibility of answering the highest-priority questions for treatment of TB.

	Timeframe (years)			Feasibility		
	<5	6 -10	>10	Moderate	Good	Excellent
What are the best methods for defining the optimal combination (bactericidal and sterilizing activities of combinations) of existing and novel drugs for shortening treatment of MDR- and XDR- TB?	X				X	
How can we ensure optimal treatment duration and dosage of all TB drugs in children of all ages (including those < 2 years and infants < 3 months), whether they are HIV infected or not, taking into account differences in absorption, distribution and excretion of pharmacological agents in children?	X				X	
What are the key drug–drug interactions of existing and new TB drugs in HIV-infected and -uninfected children of different ages? What are the effects of malnutrition and co-administered antiretroviral agents?	X				X	
What is the optimal timing of initiation of ART in HIV-infected people with active TB to prevent the immune reconstitution inflammatory syndrome while still providing optimal, life-saving ART?	X				X	
What is the interaction between existing second-line TB drugs and antiretroviral drugs, and how can adverse events be best recognized and managed?	X				X	
What are the safety, efficacy and optimal dosage of rifabutin? What are its drug interactions in TB treatment? How can we best prevent acquired rifamycin-resistant failure in HIV-infected people receiving ART?	X				X	
What is the optimal TB preventive therapy in terms of efficacy, safety, tolerability and duration of protection that can be used in HIV-infected adults and children, particularly those receiving ART?	X				X	
What are the contributions and mechanisms of action of currently used anti-TB drugs and of agents in development or in clinical trials against <i>M. tuberculosis</i> , and how can these be combined to improve treatment efficacy?	X	X			X	
Which bacterial gene mutations predict resistance to second-line drugs, and what is the clinical importance of mono-resistance and cross-resistance between second-line drugs measured in vitro?	X				X	
What are the optimal dosage, safety and efficacy of novel TB drugs (in all populations, including children and HIV-infected people)? How can existing and novel TB drugs be optimally combined into safe, well-tolerated multidrug regimens that minimize drug–drug interactions and ensure an effective (i.e. relapse-free) cure?		X				X

	Timeframe (years)			Feasibility		
	<5	6 -10	>10	Moderate	Good	Excellent
	What are the optimal length and dosage of rifamycin-based TB treatment in children and in people living with HIV? Are the currently recommended doses too low? How can the sterilizing activity be maximized, and what would be the effect of higher dosages on safety, toxicity and interactions with other TB drugs or ART?		X			
What is the optimal length of novel TB treatments for all populations, and the optimal time to start treatment in HIV-infected patients?		X			X	
What are the optimal dosage, safety and efficacy of novel drugs against drug-resistant TB? How can existing and novel drugs against drug-resistant TB be optimally combined to minimize drug–drug interactions and to ensure an efficacious (i.e. relapse-free), safe, well-tolerated multidrug regimen?		X			X	
What is the optimal duration of combined treatment containing newly introduced drugs against drug-resistant TB?		X			X	
What are the optimal drug combinations in terms of tolerability, efficacy, safety and adherence for contacts of patients with MDR-TB, including children and HIV-infected people?		X			X	
What are the optimal time for initiation and the best administration schedules of preventive TB therapy in HIV-infected patients receiving ART or not (i.e. repeated courses or lifelong preventive therapy), especially pregnant and breastfeeding women and children?		X			X	
Can novel drugs rapidly kill latent or persisting bacilli in people with latent TB infection? If so, how should they be optimally combined to introduce a safer, shorter, more efficacious preventive drug regimen for adults and children (including HIV-infected people and patients receiving ART)?		X	X	Human studies	Mouse studies	
Which biomarkers or combination of markers will help to measure the treatment effect that correlates with bactericidal and sterilizing activities of tested drugs, in order to allow shortening of clinical trials?		X		X		
How can drug combinations that include new drugs be optimally tested early enough in overall drug development? What model of drug testing should be used to investigate drug combination regimens (including fixed-dose combinations) and drug–drug interactions early in the drug development plan?		X		X		
Can we facilitate modern cell- and target-based drug discovery by (i) developing systems biology models of mycobacterial metabolism and physiology; and (ii) identifying a quantitative, reproducible, accurate, experimentally tractable, operational definition of bacterial death?		X				X

5. VACCINES

5.1 Background

The introduction of new, effective TB vaccines and vaccination strategies is crucial for meeting the TB elimination target. In the face of the emergence of drug-resistant strains of *M. tuberculosis* and the dual pandemics of TB and HIV, there has never been a more urgent need for a new vaccine that would prevent all forms of TB (32-34). Today's vaccine, BCG, provides protection against disseminated forms of TB in infants and children (TB meningitis and miliary TB) (35), but its efficacy against adult pulmonary TB is subject to large, poorly understood variation (36). In addition, BCG is not recommended for use in HIV-infected infants because of the risk for disseminated BCG disease. Many questions about the efficacy and use of BCG remain unanswered, and further research is needed, as licensing of a new prime vaccine will take time (34), and new vaccines may actually supplement BCG.

The past decade has seen great progress in TB vaccine development, including a new set of candidate TB vaccines (37), new delivery platforms and development of capacity and infrastructure for large-scale trials and vaccine production. In parallel, epidemiological cohort studies of infants and adolescents are under way in several countries, which will provide important baseline data on TB incidence and help determine the suitability of sites for large-scale efficacy trials (34). Still lacking, however, is sound knowledge of what constitutes protective immunity in TB and the best vaccine antigens and methods of delivery (38). The issue of vaccination strategies (i.e. pre-exposure, post-exposure) must also be addressed. A number of important research and development questions should be answered to allow development of more effective TB vaccines and to stimulate continuous development of new and better candidate TB vaccines.

5.2 Overall goal

To conduct research and development that result in a safe, effective, affordable vaccine to prevent all forms of TB in all age groups and that

is safe for people with HIV and other forms of immunosuppression

5.3 Major research priorities and questions

5.3.1 Conduct fundamental research as a basis for the development of effective TB vaccines.

The objective of fundamental research in vaccine development is to establish the necessary knowledge base to understand how to prime, boost or modulate the host immune response to control *M. tuberculosis* infection and disease. For this, we must determine the components of the host immune system that are critical for control and elimination of the bacteria and why prior infection and disease do not fully protect against

recurrent TB. Once infected, most humans do not develop disease, but in some the mechanism(s) of natural protection fail, leading to the development of disease. In others, *M. tuberculosis* may persist in a latent form and may subsequently become reactivated during an immunosuppressive episode (17, 21). Furthermore, as TB can develop in humans more than once in a lifetime, it would appear that the immune system does not recognize *M. tuberculosis* effectively and does not protect the body against reinfection or a second episode of disease. This makes development of an effective vaccine challenging.

Highest-priority questions:

- What are the respective roles of innate and adaptive immunity for the elimination of *M. tuberculosis*?
- How can we better understand the immune responses in various populations (HIV-infected and uninfected; various ages, from infancy to adolescence and adulthood) so as to devise optimal strategies for vaccination?
- Can a response, or a range of responses, be identified that correlates well with protective immunity after vaccination or natural TB infection? Are there significant differences between immune responses induced by vaccination and those induced by natural infection?

High-priority questions:

- Is cell-mediated immunity the only relevant immune response to *M. tuberculosis* infection or do antibodies, particularly mucosal antibodies, have a role in preventing stable infection?
- What antigens and which components of immunodominant antigens, in addition to those expressed by *M. tuberculosis* during the natural course of infection, should be added to vaccines to provide protection? Are these antigens specifically associated with different stages of disease?⁶
- Should vaccination strategies be designed to modulate networks involved in T cell regulation and memory rather than simply modulating effector mechanisms?

5.3.2 Conduct research and clinical testing to better understand the safety and efficacy of BCG and candidate vaccines.

Evaluating new BCG and other candidate vaccines first in animal models and then in different human populations and age groups after administration by different routes and in different doses will provide information for the development of new vaccines and optimization of current vaccines.

⁶ A similar question was posed in the report of the WHO/TDR Disease Reference Group on TB, Leprosy and Buruli Ulcer: “What are the optimal vaccine antigens (immunodominant and non-immunodominant), what is their interaction with the immune system, what role might they have in protection, and what should be the optimized antigen delivery/adjuvant design?”

Highest-priority questions:

- What are the similarities and differences in immune responses elicited by a new candidate vaccine or new BCG in different human populations and age groups, and within populations? How do these compare with what is measured in humans who are latently or actively infected with *M. tuberculosis* or in animal models of TB infection and disease?
- How does the mode of delivery influence the immune responses elicited by TB vaccines, including BCG?

5.3.3 Develop standardized assays and identify suitable biomarkers for use in clinical trials to measure correlates of protection.

Currently, there are no reliable biomarkers of vaccination-induced protection. As a result, expensive, large-scale studies have to be conducted to determine efficacy. A biomarker that could be validated and used as a surrogate to predict whether a vaccine will be effective is a critical long-term need. Biomarkers, or a combination of markers, should be identified by hypothesis-driven approaches and validated in phase IIb or III trials of new vaccines that prove to be effective.

Highest-priority questions:

- How can we best determine correlates of protection for vaccines?
- Which outcome measures and immunological read-outs should be considered in clinical trials that can be fully harmonized for comparisons of trials?

High-priority question:

- What would be the minimal requirements for assays of vaccine-induced immunogenicity that could be used in all vaccine trials to allow better comparison of candidate vaccines in different settings? Should these assays be both vaccine- and population-specific?

5.3.4 Develop new pre- and post-exposure vaccines, new adjuvants and new delivery platforms.

In addition to its limited efficacy as a single vaccine, the currently licensed *M. bovis* BCG is not safe for HIV-infected infants. New proposed vaccine strategies consider inducing better and longer lived T-cell immunity through re-stimulation (boost) of the immunity primarily induced by the BCG prime immunization at a later stage in life (in childhood or at adolescent age) using a newly developed vaccine. Important knowledge can be drawn from better understanding of BCG vaccine, its advantages and limitations, and whether its efficacy might be improved, particularly by studying new recombinant replacement vaccines for BCG. It is therefore important to evaluate new, safe, prime (pre-exposure) and boost (post-exposure) vaccines, with novel delivery systems and adjuvants and to identify those vaccine combinations that induce an 'optimal' immune response.

5.3.4.1 Develop pre- and post-exposure vaccines that can be associated in various vaccination strategies.

High-priority questions:

- What are the optimal conditions for prime–boost strategies for different target populations (duration of intervals, boosting dose and number of boosts)?
- What are the best TB prime or boost vaccines and the best combinations of prime and boost vaccines in the pipeline in terms of immune response, safety and efficacy for all target populations, including HIV-infected children and people living with HIV or other immunosuppressive conditions?

5.3.4.2 Optimize adjuvants to improve vaccine uptake.

High-priority question:

- How does the interaction of the adjuvant(s) with the innate immune system determine the outcome of the T-cell activation required for an effective TB vaccine?

Medium-priority question:

- How can the effectiveness and safety of mucosal adjuvants be improved to support the development of mucosal vaccines?

5.3.5 Improve and standardize preclinical assays to evaluate the immunogenicity and potential protective efficacy of new TB vaccines.

Current animal models have several limitations; for instance, mouse models may not reflect human disease, and non-human primates that may reflect human disease quite well are very expensive and their use raises ethical issues. Also, certain preclinical tests are required for regulatory approval. As a result, diverse approaches to preclinical testing of new TB vaccine candidates are reported in the literature, making comparisons difficult. New, affordable, standardized animal models of TB infection and disease are therefore required. Furthermore, new tests that can predict in animal models which vaccines are likely to be effective in human target populations are also needed.

Highest-priority questions:

- Which preclinical tests are critical for determining whether a new candidate vaccine should move forward into clinical testing?
- What is the potential of existing or novel preclinical model systems (primarily animal models) to assess preclinically the protective efficacy and immunogenicity of new vaccines, in both pre- and post-infected human populations?

5.3.6 Improve and standardize testing of TB vaccines in clinical trials.

Vaccine trials differ from drug trials in that the product is given to healthy people to protect them against a condition that is supposed to be averted. Accurate knowledge is therefore needed of that condition in the general population as well as in specific age groups and high-risk groups. The information includes baseline mortality (all causes and cause-specific) and morbidity and estimates of TB incidence in various cohorts (infants, children, adolescents, adults, HIV-infected people). A good understanding of the epidemiology of TB at trial sites is therefore required as a basis for trial designs and sample size calculations. In addition, it is still unclear what is the best end-point to use in efficacy trials, particularly in infants and HIV-infected adults. The proportion of TB cases in infants and HIV-infected adults that meet the end-point criteria for definite TB, required for licensure trials, is substantially lower than for all TB end-points, e.g. probable and possible TB. Better tests are required to increase the proportion of

TB cases that meet the criteria for definite TB. Lastly, there is currently limited capacity for phase IIb and III clinical trials worldwide, and the number of sites with capacity to evaluate new vaccines in infants, adolescents and HIV-infected adults should be scaled up. Novel clinical trial designs are needed to shorten the time to licensure of an effective vaccine.

5.3.6.1 Conduct pre-vaccine epidemiological studies to assess the incidence of TB, especially in infants, adolescents and people with HIV-associated TB.

Highest-priority question:

- How can pre-vaccine epidemiological studies best prepare for TB vaccine development and implementation? What novel methods can be used?

5.3.6.2 Conduct and standardize clinical trials of candidate vaccines in both HIV-infected and uninfected populations, in *M. tuberculosis* post-infected individuals and in BCG-vaccinated patients, as appropriate.⁷

Highest-priority questions:

- How can the definition of clinical end-points for vaccine trials be improved, particularly for infants and HIV-infected individuals?
- Are live vaccines and attenuated *M. tuberculosis* strains safe for infants, children and adults? How can this best be proved?

High-priority questions:

- How can clinical sites for TB vaccine trials best be standardized?
- How can phase III vaccine trials be shortened? Are there alternative models that rely on detection of immune protection?

5.3.6.3 Develop the appropriate infrastructure to support clinical vaccine trials in high-burden settings and assure enrolment of sufficient numbers of people to address immunological responses that may vary by region, including settings with different HIV seroprevalence.

High-priority question:

- What infrastructure is necessary for a large-scale clinical trial site for TB vaccines?

Medium-priority question:

- How can large-scale clinical trial sites be most efficiently planned (including location, background level of TB, surveillance and laboratory capabilities, isoniazid preventive therapy) in order to reduce changes in epidemiological and TB control strategies during the trial?

⁷ Including infants, neonates, adolescents and adults

Key messages

- The top priority research areas are:
 - (i) identification of correlates of protective immunity after vaccination;
 - (ii) identification of the immunodominant antigens associated with different metabolic states of *M. tuberculosis* (or components of these antigens) to be added to vaccines to increase protection;
 - (iii) determination of appropriate clinical end-points and immunological read-outs for vaccine trials (especially with children); and
 - (iv) search for novel model systems for preclinical and clinical (challenge model) testing of TB vaccines, including pre- and post-exposure models and models that mimic reactivation.
- Priorities in fundamental research for vaccine development should aim at determining the components of the host immune system that are critical for control and elimination of the bacilli. This will involve determining the respective roles of innate and adaptive immunity in preventing *M. tuberculosis* infection and reactivation of latent disease and better understanding of immune responses against different metabolic stages of the pathogen and in different populations (HIV-infected and uninfected; various ages, from infancy to adolescence and adulthood).
- A high priority is development of improved vaccines for prime–boost vaccination strategies (including improvement of BCG as prime) and their optimal conditions of use (duration of intervals, boosting dose and number of boosts).
- This will require better understanding of the immune responses to BCG and new vaccines (including a comparison of responses obtained in different preclinical animal models).
- Identification and standardization of assays to assess vaccine-induced immunogenicity are critical to allow better comparison of candidate vaccines in different settings.
- Epidemiological studies to facilitate TB vaccine development and implementation of vaccine trials are a high priority.
- In the longer term, suitable methods for standardizing and planning trials sites should be identified.

TABLE 6. Estimated timeframe and feasibility of answering the highest-priority questions for research on TB vaccines.

	Timeframe (in years)			Feasibility			
	<5	6 -10	>10	Moderate	Good	Excellent	
	Which preclinical tests are critical for determining whether a new candidate vaccine should move forward into clinical testing?	X					X
	Are live vaccines and attenuated <i>M. tuberculosis</i> strains safe for infants, children and adults? How can this best be proved?	X					X
How can the definition of clinical end-points for vaccine trials be improved, particularly for infants and HIV-infected individuals?	X				X		
What are the similarities and differences in immune responses elicited by a new candidate vaccine or new BCG in different human populations and age groups, and within populations? How do these compare with what is measured in humans who are latently or actively infected with <i>M. tuberculosis</i> or in animal models of TB infection and disease?	X				X		
Which outcome measures and immunological read-outs should be considered in clinical trials that can be fully harmonized for comparisons of trials?	X			X			
What are the optimal conditions for prime-boost strategies for different target populations (duration of intervals, boosting dose and number of boosts)?		X			X		
What is the potential of existing or novel preclinical model systems (primarily animal models) to assess preclinically the protective efficacy and immunogenicity of new vaccines, in both pre- and post-infected human populations?		X			X		
How can pre-vaccine epidemiological studies best prepare for TB vaccine development and implementation? What novel methods can be used?		X			X		
How can we best determine correlates of protection for vaccines?		X		X			
How can we better understand the immune responses in various populations (HIV-infected and uninfected; various ages, from infancy to adolescence and adulthood) so as to devise optimal strategies for vaccination?		X			X		
What are the respective roles of innate and adaptive immunity for the elimination of <i>M. tuberculosis</i> ?		X		X			
Can a response, or a range of responses, be identified that correlates well with protective immunity after vaccination or natural TB infection? Are there significant differences between immune responses induced by vaccination and those induced by natural infection?		X			X		

6. OPERATIONAL AND PUBLIC HEALTH RESEARCH

6.1 Background

While better TB control cannot be achieved without solid knowledge about the causative organism and its relation to humans, the social and health system context within which TB continues to flourish must also be understood (39). Continued investment is needed in fundamental understanding of human behaviour (both health-care providers and consumers) and of health system organization and dynamics in relation to TB. The social science and organizational psychology of health systems are equally crucial to maximize the benefits of both existing and new tools and are therefore essential components if the target of elimination is to be met.

Operational research is necessary to optimize all aspects of TB control, including access to accurate diagnosis, effective treatment and optimal coverage with vaccination against *M. tuberculosis*, and to address the challenges posed by drug resistance and HIV infection (40). In its broad sense, operational research covers a wide spectrum of activities, from local research to improve TB control programme performance, to national and international policy-guiding research, including the assessment of new interventions to improve TB control (effective

and efficient use of new and existing tools and determination of the conditions and requirements under which they can be effectively implemented) (41).

The type and scale of operational research depends largely on the questions being addressed, the level of care and users concerned, and the expected relevance of the results. At national level, TB control programmes should design setting-oriented operational research projects to address local problems and recommend appropriate solutions, involving partners at all stages and levels. Research should also address the obstacles to integration of HIV and TB care by national programmes. At international level, a robust evidence base is increasingly recommended for guiding policy-making (including the use of systematic reviews and GRADE evaluation); therefore, multicentre operational research projects are needed to address some of the gaps, which would lead to international policy changes (41). The following areas and priority questions have been identified to address the obstacles that hamper essential TB control activities or appropriate implementation of innovative technologies and novel service delivery models.

6.2 Overall goal

To conduct research for evaluating and improving TB control programme performance and designing interventions that result in improved policy-making,

better implementation in health systems and more efficient and effective methods of service delivery.

6.3 Major research areas and priority questions

The following areas and priority questions have been identified to address the gaps that limit essential TB control activities or appropriate implementation of innovative technologies and novel service delivery models.

6.3.1 Improve TB case detection and diagnosis.

Operational research is needed to improve access to and use of diagnostic services in order to increase early TB case-detection and improve the diagnosis

of drug-sensitive TB, MDR- and XDR-TB and TB–HIV coinfection.

6.3.1.1 Case-finding

Case-finding is the cornerstone of the current TB control strategy. Unless programmes can find cases, transmission of TB in communities cannot be interrupted. Passive case finding alone has been shown to be inadequate to control TB, and other approaches, such as enhanced or active case-finding, can substantially improve case detection and diagnosis when added to routine facility-based DOTS (42, 43). Such approaches can also be useful in settings with a high HIV prevalence. Further operational research is needed to identify how best to enhance case-finding in different epidemiological settings.

Highest-priority questions:

- What are the health system, community and patient barriers to case finding (both at the social and operational levels) in various populations, and which interventions would be most effective in overcoming these barriers?
- What are the best operational models for enhanced TB case-finding among HIV-infected patients in HIV service facilities and at community level, in settings with high and low HIV prevalence?
- Which high-risk populations should be screened for drug-susceptible, MDR- and XDR-TB; when should they be screened, and for what should they be screened?
- Does increased case-finding lower mortality and decrease transmission from cases?

6.3.1.2 New programmatic approaches for TB diagnosis

Further to WHO’s recent endorsement of the new diagnostic tool Xpert MTB/RIF, operational research is needed to determine its precise role in the diagnosis of TB in various settings, so as to optimize its use and scale-up. In parallel, approaches to improve case detection rates, such as front-loaded microscopy, fluorescence microscopy and measures to ensure that all patients with smear-positive TB are captured in TB treatment registers, should also be investigated (44-47). Operational research is needed to test revised clinical algorithms for TB diagnosis and to help define the most effective

use of new diagnostic tools in specific settings and populations (e.g. screening or confirmatory, rule-in or rule-out), so as to maximize their impact.

Highest-priority questions:

- What evidence is required for scaling up new diagnostics? How should evidence for scaling up and impact be obtained?
- What are the minimum requirements for health systems for introducing and scaling up new diagnostics for TB in various health systems?
- How can diagnostic services be brought nearer to the community (e.g. decentralization, active case-finding, mobile systems)? How effective are these methods, and how can they be integrated into the general health system, including HIV and maternal and child health programmes?

6.3.1.3 Assess the validity of the various TB screening algorithms in different settings.

Most resource-limited settings rely on algorithms based on symptoms, smear microscopy, chest X-ray and response to TB treatment, to diagnose TB. The most consistently discriminating symptom-based screening algorithm recently advocated for identification of TB among people living with HIV (rule-out) includes “cough of any duration, weight loss, fever and night sweats” (48). Recent TB prevalence surveys, however, identified people with culture-positive TB who did not report any TB symptoms at all. The role of chest radiography is controversial, some studies showing value and others showing none (49, 50). The diagnosis of smear-negative TB (rule-in algorithm) in both adults and children continues to be problematic (51). Many programmes have locally validated algorithms based on clinical features, antibiotic response and chest radiography, but these are insensitive and non-specific, resulting in many false-positive and false-negative diagnoses, especially in people living with HIV.

Highest-priority questions:

- Which high-risk populations should be screened for drug-susceptible, MDR- or XDR-TB; when should they be screened, and for what should they be screened?
- In high-risk populations, how can we best rule out active TB by screening?

- What are the best algorithms for selecting patients eligible for drug susceptibility testing and second-line treatment in different settings?

High-priority questions:

- What are the optimal algorithms for diagnosing all forms of TB in terms of sensitivity, specificity and predictive value, that would be applicable for screening in various settings (high-risk populations, people living with HIV, children, asymptomatic patients) and would eliminate diagnostic delay?
- How can improved clinical algorithms be applied in routine settings to increase the number of smear-negative TB cases detected and treated?
- What are the most effective strategies for promoting and scaling up integrated screening of HIV and TB infection and disease among close contacts of HIV-infected TB patients?
- Is there a role for digital X-ray in routine programme algorithms, and is there a role for automated reading of digital X-rays in routine programme operations?

6.3.2 Investigate methods to improve access to treatment and treatment delivery for drug-sensitive and drug-resistant TB.

Although DOTS is the accepted standard of care for TB, successful treatment outcomes remain low in some parts of the world. Research is required to assess the behavioural and social factors among health workers, patients and communities in relation to treatment and re-treatment and in terms of access, adherence and treatment outcomes. For MDR-TB, WHO guidelines recommend 18–24 months of treatment after culture conversion, with at least four drugs known to be effective when drug susceptibility testing is available (52). In the most recent WHO TB surveillance report (53), however, most country cohorts were too small to allow reliable estimates of treatment outcomes in patients with MDR-TB, reflecting poor access to treatment. Given the urgent need to increase access to treatment for MDR-TB, careful evaluation of treatment strategies is vital to ensure that the most effective, feasible approaches are used, particularly in low-income settings, where most cases of MDR-TB are found.

Highest-priority questions:

- Can new technologies (e.g. mobile phones) be effectively used to improve treatment adherence?
- What are the best strategies for scaling up drug-resistant TB management into TB control programmes with provision of second-line treatment (e.g. inpatient or ambulatory treatment, use of incentives and ‘enablers’ to enhance adherence to treatment, social support, community involvement)?

High-priority questions:

- What are the relative proportions of different subgroups of previously treated patients (failed first-line treatment or subsequent course of therapy; returned after defaulting; relapsed) among patients who develop MDR- or XDR-TB?
- What are the management, staffing and procurement policies that lead to stock-outs? To what extent and under what conditions do stock-outs result in poor treatment outcomes and/or acquisition or amplification of drug resistance?
- What are the bottlenecks for scaling up access to drug-resistant TB treatment in different settings?

6.3.3 Institute sustainable collaboration with all private and public providers of TB care and control.

A ‘public–private mix’ is defined as all health-care providers, public and private, involved in the provision of TB diagnostic and treatment services. TB patients in many TB-endemic countries, including the very poor, seek care from a wide variety of health-care providers. The public–private mix DOTS model expands coverage of TB services by using all available non-state and public sector health-care providers to deliver TB services to populations at risk (54, 55). Further operational research is needed to optimize collaboration with non-programme providers.

Highest-priority question:

- Which public–private mix models and approaches (such as the use of incentives and ‘enablers’, regulatory approaches and social marketing and franchising) are appropriate for nationwide scaling-up?

High-priority questions:

- What are the potential contributions of different care providers to TB control in improving users' access, case detection and outcomes for underserved groups, and for reducing diagnostic delay and cost of care?
- How can the rational use of new diagnostics and drugs in the private sector be ensured?

6.3.4 Address priority operational research questions at global, regional or national level to improve implementation of collaborative TB and HIV activities.

Integration of TB and HIV services to deliver collaborative care is important in settings where many TB patients are also infected with HIV and therefore need ART. A recent systematic review showed that widely different models of integration of services are being implemented: (i) TB services refer patients for HIV testing and treatment; (ii) HIV services refer people living with HIV for TB screening and treatment; (iii) TB services test patients for HIV and refer them for treatment; (iv) HIV services screen for TB and refer patients for treatment; and (v) TB and HIV services are provided at a single facility (56). It is not known which delivery model is the best, and it is unlikely that a 'one size fits all' approach will work well in all settings. Operational research is needed to derive evidence on the best service delivery models and on their effectiveness in enhancing the uptake of TB and HIV prevention, diagnosis and treatment for people affected by both diseases.

Highest-priority questions:

- How can the organization and provision of TB treatment and ART be optimally combined in health centres, TB programmes and HIV programmes for better TB and HIV control (including screening for TB, initiation of isoniazid preventive therapy, early start of ART and infection control)?
- In people living with HIV and initiating isoniazid preventive therapy (or novel preventive TB treatments), what models of medication delivery, clinical monitoring and community support reduce the rates of default during prevention therapy, the incidence of breakthrough TB and the occurrence of severe adverse events?

High-priority questions:

- How can joint TB and HIV interventions best be integrated and cost-effectively delivered at community and health sector levels and in settings with different TB and HIV epidemiological status?
- Does 'very early' initiation of ART (i.e. using the 'test and treat' strategy) reduce the risk for TB in individuals and improve TB control in settings with a high HIV prevalence?
- How can programmes for preventing mother-to-child transmission be used to ensure appropriate TB screening of HIV-infected and uninfected women during pregnancy? How can such programmes post partum be used to ensure screening of HIV-infected women and their exposed infants for TB?

Additional questions (from the Disease Reference Group):

- What are the barriers to adherence to treatment, and what interventions improve adherence to HIV and TB treatment of TB-HIV coinfecting people?
- What are the barriers (of policy-makers, service providers and patients) to implementation of isoniazid preventive therapy for people living with HIV?

6.3.5 Design collaborative activities in other disease programmes or situations in which TB risk is increased.

A growing body of literature confirms that smoking and diabetes are important risk factors for TB, but these associations are still largely unrecognized by clinicians and public health practitioners (57). Diabetes medication may interact with anti-TB drugs (rifampicin in particular), with corresponding complications in glycaemia control. The increase in the burden of diabetes and other chronic diseases in developing countries make it likely that more people will contract both diabetes and TB. India accounts for one fifth of newly diagnosed TB patients worldwide, of whom almost half are estimated to have diabetes (57).

Highest-priority question:

- What are the feasibility and effectiveness of bi-directional TB screening in TB and diabetes clinics?

High-priority questions:

- What are the effects of diabetes and its control and of smoking cessation on standardized TB treatment outcomes?
- What is the value of TB screening strategies in antenatal and HIV maternal and child programmes?

6.3.6 Investigate methods to encourage community participation to increase the effectiveness of all interventions (e.g. case-finding, access to treatment and care delivery).

High-priority question:

- How can we best involve communities in research on new interventions, including the design, ethical evaluation, protection of human subjects, undertaking of research, interpretation of findings and dissemination of findings?

Additional question (from the open web-based survey):

- What are the societal factors that influence the effectiveness of interventions; for example, do geopolitical structures affect access and overall management of TB control programmes and what are the social perspectives of disease (e.g. the usefulness of different campaign methods to increase social awareness about TB and whether these methods influence societal norms and impressions of the disease)?

6.3.7 Optimize infection control to reduce TB transmission.

Exposure to tubercle bacilli in health-care facilities accounts for an appreciable but undetermined proportion of the total risk for TB infection, especially among people living with HIV/AIDS, who repeatedly attend clinics for chronic care. Infection control relies mainly on early identification and prompt isolation and treatment of suspected cases of TB, combined with facility engineering and patient organization to avoid congestion and ensure appropriate air and patient flow in facilities. The WHO TB infection control guidelines were updated in 2009 (57), and operational research is needed to assess how extensively these have been adopted and implemented, and their

practical effectiveness. More research is needed on the importance of environmental control measures in reducing or preventing nosocomial TB transmission in crowded health-care settings, particularly in models of better implementation of joint HIV and TB care.

Highest-priority questions:

- What are the impact and effectiveness (including cost-effectiveness) of individual infection control measures in reducing TB transmission in general and specialized health-care settings, in households and in the community?
- What is the best combination of infection control interventions to reduce *M. tuberculosis* transmission effectively, and how should these measures be implemented and monitored in health-care settings, in households and in the community?

Medium-priority question:

- What surveillance or clinical criteria will result in rapid identification and control of facility-based MDR- and XDR-TB outbreaks?

6.3.8 Improve measurement of disease burden by effective surveillance, monitoring and evaluation of TB programmes.

The importance of accurate measurement of the burden of TB cannot be overstated. The prevalence, incidence and mortality of TB must be accurately measured in the general population and in vulnerable populations. This information is vital to TB programmes for planning purposes (e.g. estimation of drug requirements) and to evaluate the effectiveness of control interventions. TB epidemiology is discussed in Chapter III, section 3; listed below are research questions that can be embedded in routine health data collection.

High-priority questions:

- What are the best tools for measuring TB burden (morbidity, mortality) in limited-resource countries?
- What is the best programmatic model for surveillance of TB control in terms of epidemiology and management?

6.3.9 Ensure that countries have the capacity to perform TB-related operational research to improve TB programme performance.

Operational research is the main means for improving programme activities and determining how policies can be shaped for implementation and subsequent evaluation (41). Research capacity must be developed, specific resources allocated and stakeholders brought together to promote this important component of research.

Highest-priority question:

- How can trained research staff be acquired and retained in programmes?

High-priority questions:

- What are the effectiveness and impact of existing training models in terms of products and outcomes (i.e. number and type of publications, training completed, impact indicators for policy and practice), and what can we learn from them?
- What sort of efficient funding mechanism is needed for operational research capacity-building at national level, with an international or consortium community of practitioners, facilitators, mentors, a standard curriculum and sustained mentorship?

Key messages

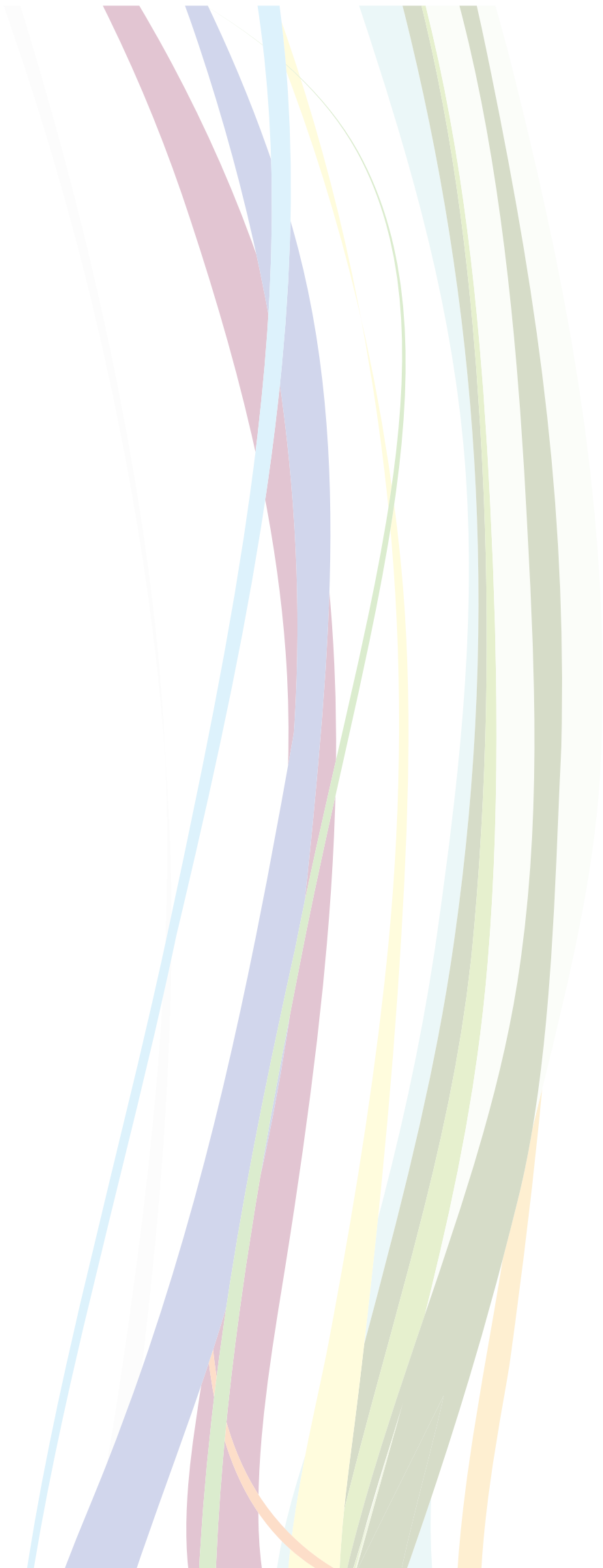
- Operational research is increasingly being recognized as an important area in TB control, as it helps to improve TB control locally or nationally and also helps to guide policy recommendations at national and international levels.
- High-priority questions relate to TB case-finding and screening, access to diagnostics, treatment access and delivery, TB-HIV programme interactions and infection control. These questions must be addressed both in the general context of health services and for specific high-risk groups (TB-HIV co-infection, people with MDR-TB, children, prisoners, etc).
- Of highest priority are the following research topics:
 - investigation of methods and means to optimize TB case-finding and measure impact of intensive case-finding on mortality and other outcomes, particularly among HIV-infected and other vulnerable populations, particularly infants and children;
 - identification of best screening algorithms and scale-up of new TB diagnostic tools to improve case detection, particularly among people living with HIV and suspected cases of MDR-TB;
 - development of methods and means to scale up isoniazid preventive therapy under field conditions and in HIV clinics delivering ART;
 - development of strategies to strengthen the links between TB and HIV control programmes at all levels of health care, with optimal integration of interventions
 - identification of strategies to scale-up access to MDR- and XDR-TB treatment in resource-limited settings and improve treatment outcomes, whether or not associated with ART;
 - integration of TB care with that of chronic diseases, with particular emphasis on diabetes;
 - development of methods to expand access to treatment for vulnerable and marginalized groups by making use of private or alternative health care providers;
 - determination of the efficacy of individual TB infection control measures in resource-limited settings and strategies to implement, monitor and evaluate TB infection control in health facilities, communities and households;

TABLE 7. Estimated timeframe and feasibility of answering the highest-priority questions for TB operational and public health research.

	Timeframe (years)			Feasibility*		
	<5	6 - 10	>10	Moderate	Good	Excellent
What are the health system, community and patient barriers to case finding (both at the social and operational levels) in various populations, and which interventions would be most effective in overcoming these barriers?	X				X	
What are the best operational models for enhanced TB case-finding among HIV-infected patients in HIV service facilities and at community level, in settings with high and low HIV prevalence?	X				X	
Which high-risk populations should be screened for drug-susceptible, MDR- and XDR-TB; when should they be screened, and for what should they be screened?	X				X	
What evidence is required for scaling up new diagnostics? How should evidence for scaling up and impact be obtained?	X				X	
What are the minimum requirements for health systems for introducing and scaling up new diagnostics for TB in various health systems?	X				X	
How can diagnostic services be brought nearer to the community (e.g. decentralization, active case-finding, mobile systems)? How effective are these methods, and how can they be integrated into the general health system, including HIV and maternal and child health programmes?	X				X	
In high-risk populations, how can we best rule out active TB by screening?	X				X	
What are the best algorithms for selecting patients eligible for drug susceptibility testing and second-line treatment in different settings?	X				X	
Can new technologies (e.g. mobile phones) be effectively used to improve treatment adherence?	X				X	
What are the best strategies for scaling up drug-resistant TB management into TB control programmes with provision of second-line treatment (e.g. inpatient or ambulatory treatment, use of incentives and 'enablers' to enhance adherence to treatment, social support, community involvement)?	X				X	

	Timeframe (years)			Feasibility*			
	<5	6 -10	>10	Moderate	Good	Excellent	
	How can the organization and provision of TB treatment and ART be optimally combined in health centres, TB programmes and HIV programmes for better TB and HIV control (including screening for TB, initiation of isoniazid preventive therapy, early start of ART and infection control)?	X				X	
	In people living with HIV and initiating isoniazid preventive therapy (or novel preventive TB treatments), what models of medication delivery, clinical monitoring and community support reduce the rates of default during preventive therapy, the incidence of breakthrough TB and the occurrence of severe adverse events?	X				X	
What are the feasibility and effectiveness of bi-directional TB screening in TB and diabetes clinics?	X				X		
What are the relative proportions of different subgroups of previously treated patients (failed first-line treatment or subsequent course of therapy; returned after defaulting; relapsed) among patients who develop MDR- or XDR-TB?		X			X		
Does increased case-finding lower mortality and decrease transmission from cases?		X			X		
What is the best combination of infection control interventions to reduce <i>M. tuberculosis</i> transmission effectively, and how should these measures be implemented and monitored in health-care settings, in households and in the community?		X			X		
Which public-private mix models and approaches (such as the use of incentives and 'enablers', regulatory approaches and social marketing and franchising) are appropriate for nationwide scaling-up?		X		X			
How can trained research staff be acquired and retained in programmes?				X			
What are the impact and effectiveness (including cost-effectiveness) of individual infection control measures in reducing TB transmission in general and specialized health-care settings, in households and in the community?				X			

* for several experts, feasibility was considered to vary quite substantially according to target group, settings and conditions



IV. DISCUSSION

The prioritization of research questions was carried out by the Research Movement of the Stop TB Partnership between September 2009 and March 2011 in a series of activities, including expert group meetings, workshops, systematic reviews, wide circulation and consultation of stakeholders, and final ranking by a large group of independent worldwide experts. The process was part of an action plan to address the two main objectives of the Research Movement, i.e. to provide leadership and advocacy to mobilize increased resources in support of a coherent and comprehensive global TB research agenda; and to provide a forum for funders and implementers of TB research to coordinate plans and actions.⁸

The detailed questions and their ranking according to the two analyses are shown in **Annexes V and VI** (which will be published on the Research Movement website)⁸. Most of the questions classified as highest priorities are in line with general expectations, considering the wide agreement in the TB community on the need for new tools for better control. This document, however, clearly indicates the areas in which further research is needed across the continuum. This TB research roadmap takes its rightful place in continuation of the *Global Plan to Stop TB 2011–2015* by indicating directions for research beyond 2015, with a view to guiding research activities towards the elimination of TB.

The prioritization method used in developing this roadmap had several advantages: it was systematic (allowing technical experts and non-experts to list and score competing research options in a highly structured way), fully transparent, unbiased (experts submitted their input independently of each other), repeatable and representative (involving a large cross-section of stakeholders). Most importantly, the method included an efficient means for considering the voice of key stakeholders, who were given the possibility of adding questions at the time of priority-setting, during circulation of the initial lists of research questions arising from the various expert group meetings and workshops. Lastly, comments were given by the larger community in an open web-based survey, between December 2010 and January 2011.

The method also had limitations. It required each question to be scored in its own right and thus could not address well the interdependence of

the questions. Further, the prioritization process was often described as “complex, difficult and time-consuming”, because of the number of questions and the number of criteria against which the questions were evaluated. The questions also lacked a defined ‘hierarchy’, i.e. they were evaluated by the same criteria without considering whether they were positioned upstream or downstream in research. The questions differed in their ‘specificity’, as some were generally formulated, while others were very specialized, leading to some overlap between questions. This introduced difficulty in differentiating between ‘critical or not critical’ and ‘deliverable or not deliverable’ aspects of the questions. In addition, the prioritization criteria were sometimes difficult to grasp: deliverability depended on where a question was placed on the overall spectrum of research and development, since downstream questions, which depend on successful upstream work, are by definition more ‘deliverable’ than upstream questions. An additional ‘feasibility’ criterion could have been included, perhaps replacing the answerability and equity criteria in some research areas (for instance, fundamental research). Lastly, the fact that participants could not ignore questions might have affected the final outcome, as this meant that a large number of questions were rated as ‘probable’ for most criteria, leading to a situation of ‘regression to the mean’, which reduced discrimination.

Despite these issues, there was remarkable agreement between the weighted and unweighted analyses with regard to the highest- and high-priority questions to be addressed in research on TB, and these were also in line with the priorities set by the WHO/TDR Disease Reference Group on TB, Leprosy and Buruli Ulcer (8). As a result, the final document is a concise, coherent report that describes the major advances needed in research on TB. It should be noted that the report concentrates on tools for TB control, emphasizing the need for fundamental research on which to base the development of new tools for TB control, conducting research to develop these new tools and finally operational research to ensure effective, efficient uptake of these tools under routine programmatic conditions.

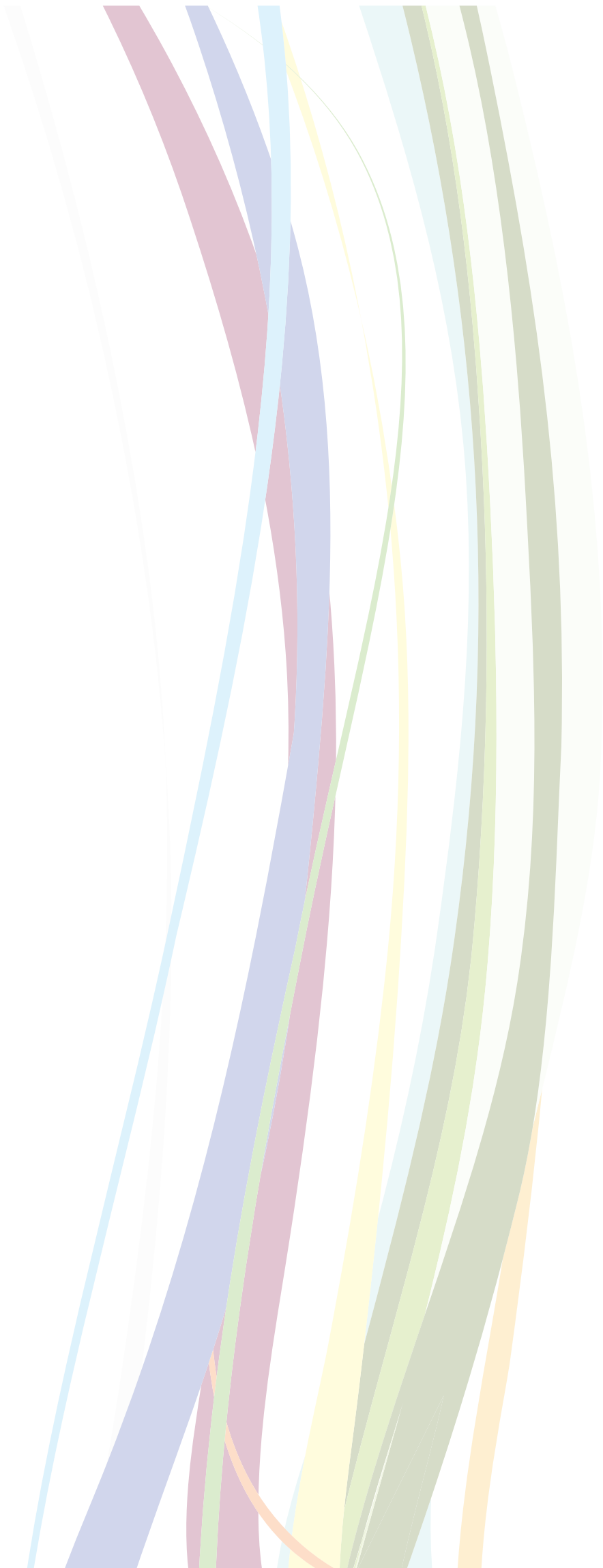
As we elected to use a holistic approach, covering the continuum of research, specific ‘cross-cutting’ or ‘transverse’ research areas, such as TB–HIV coinfection, MDR-TB and paediatric TB were not

⁸ See: <http://www.stoptb.org/global/research>.

singled out, but issues pertaining to each of these areas were systematically addressed in each selected research area. As research agendas have already been produced for these conditions (59-61), we highlighted in each research area issues that apply particularly to the problems of TB-HIV coinfection, MDR-TB and paediatric TB, within the larger framework of the most important research.

We also elected to address only the research questions and not the most appropriate methods for addressing them, as these are highly dependent on the specific questions and context. Details of methods for fundamental or operational research were given in ad-hoc expert group meetings and workshops convened to address them (see **Annex II**). A document providing suggested research methods and designs to address priorities in operational research has been developed by the TB Research Movement in collaboration with several stakeholders, including the Liverpool School of Tropical Medicine and published jointly with the WHO Stop TB Department and the Global Fund to Fight AIDS, Tuberculosis and Malaria (62). Specific design methods could also be proposed for all the research questions

described in the report; however, we consider that a multidisciplinary approach is key to developing suitable methods for addressing major questions. In this context, large-scale, multi-site, longitudinal studies are needed in populations with high exposure and in groups at high risk for disease progression (i.e. children under 5 years, household TB contacts, HIV-infected populations), from whom specimens would be collected at various stages of infection and disease for microbial and host biomarker studies. Such large, comprehensive, multicentre cohort studies would make it possible to address key questions on the natural history of TB and TB transmission in a variety of settings and populations (including high-risk groups). They would also allow the development of high-quality sample repositories of well-characterized microbial and human samples for coordinated, collaborative identification of biomarkers. They would offer the ideal circumstances for collecting information on markers of response to therapy or immune protection. In addition, they would allow further investigation of various geographical and environmental aspects, as well as issues related to different health systems.



IV. CONCLUSION

The overall objective of this global TB research roadmap was to define the essential research questions that provide a common framework for scientific disciplines to work concurrently and collaboratively for better TB control towards the elimination of TB.

As TB results from the close relation between the pathogen and the host, five basic research questions emerge:

1. *Why do only some exposed people get the disease and others do not?* This question reflects the importance of studying the natural history and epidemiology of TB.
2. *How can we identify people who are infected and people at highest risk for developing disease?* The answer to this question will provide the foundation for the development of new preventive and diagnostic strategies.
3. *How can we interrupt progression from exposure to infection and from infection to disease?* Understanding what constitutes successful control of infection by the host and what constitutes development of disease is critical for the development of diverse vaccination and other TB prevention strategies.
4. *Why do some people fail to respond fully to treatment?* Answers to this question will shed light on the mechanisms of action of current TB drugs and provide the knowledge needed to improve treatment of both drug-sensitive and drug-resistant TB.
5. *What are the biological and sociological factors that sustain transmission of TB in populations?* The response to this question will help us to identify the interventions that can most effectively interrupt transmission, a key aspect of the fight towards elimination of TB.

Responses to these questions will fill knowledge gaps and will indicate how to develop new tools for the control of TB that are safe, effective, accessible and affordable to all, so as best to prevent, detect and treat TB in all populations (including those with TB–HIV coinfection, MDR-TB and paediatric TB), and ensure their uptake by programmes in the framework of optimal control strategies (including active case-finding, optimized access to diagnosis and care, improved laboratories, improved infection control, and involvement of all health-care providers). The questions listed in this document are complex and cannot be addressed without close coordination and collaboration among all stakeholders and across disciplines. While each scientific discipline can make significant contributions to each question, the larger picture must be addressed in collaborative activities. This will allow establishment of the much-needed transformational research response to the global TB epidemic, addressing the critical questions for development of new diagnostics, drugs and vaccines and ensuring that all macro- and micro-environmental aspects are purposively addressed, so as to meet the Partnership and Millennium Development Goals by 2015 and work towards the elimination of TB by 2050. The present document, which encompasses the continuum of TB research, is designed to ensure that research is promoted and coordinated worldwide, including in the low-income countries that bear the largest burden of human suffering due to TB, and that appropriate transfer of technology occurs so that novel control tools are accessible and affordable to populations in the countries that need them most.

In view of the current state of the global TB epidemic, the present weaknesses in TB control worldwide and the need for new and improved health-care interventions to speed up the rate of decline of TB worldwide, research on TB is a crucial component of global health. This research roadmap is proposed as a vehicle and framework upon which transformational and outcome-oriented focus areas can be constructed for better TB research towards elimination of the disease.

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Annex I

List of the members of the Technical Working Group

Members of the Core Group (alphabetical order)

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Matteo Zignol	World Health Organization, Stop TB Department, Geneva, Switzerland

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Afranio Kristki	Rede Brasileira de Pesquisas em Tuberculose (REDE-TB), Rio de Janeiro, Brasil
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Annex II

Definitions of research areas

Fundamental research:

“Experimental or theoretical work that aims to acquire new knowledge of the underlying phenomena and observable facts without any particular application or use in view” (Australian Research Council).

Fundamental TB research aims at improving the knowledge base on of the TB causative agent *M. tuberculosis*, as well as on the natural history and pathology of TB in humans. Fundamental research is needed to maintain the product pipeline filled, and to ensure that a sufficient number of new product candidates and strategies enter clinical development.

Epidemiology:

The National Center for Biotechnology Information (NCBI) defines Epidemiology as “the field of medicine concerned with the determination of causes, incidence, and characteristic behaviour of disease outbreaks affecting human populations”. It includes the interrelationships of host, agent, and environment as related to the distribution and control of disease.

Operational research:

In the Public Health Dictionary, operational research (OR) is defined as “the systematic study of the way in which organizations function. This may be done by direct observation, a combination of observation and experiment, or statistical analysis of data from various aspects of the organization(s) under study. OR focuses on ways to improve the performance of both individuals and groups, and of their work setting and equipment. OR includes health services research that aims at evaluating health services, outcomes and process by which services are provided. It involves epidemiology, economics and social and behavioural sciences”.

“OR is the search for knowledge on interventions, strategies, or tools that can enhance the quality, effectiveness, or coverage of programs in which the research is being done. OR involves three main types of method: descriptive (cross-sectional, if a strong analytic component is also present), case-control, and retrospective or prospective cohort analysis.”⁹ This includes (i) health services/ health systems research, (ii) population based research, and (iii) studies on policy and advocacy.

⁹ Zachariah R et al. Operational research in low-income countries: what, why, and how? *The Lancet infectious diseases*, 2009;9 (11), 711-7

Annex III

List of Expert Group Meetings, Workshops and Systematic Reviews

I. Expert Group Meetings (EGM) and workshops

1. EGM on New Diagnostics, New Drugs and New Vaccines:
 - 12-13 September 2009, Geneva, Switzerland
 - 11th-12th January 2010, Geneva, Switzerland
2. EGM on Operational Research: 22nd February 2010, Geneva, Switzerland
3. Workshop on Operational Research: 11-12th May 2010, Geneva, Switzerland.
4. Workshop on Fundamental Research, 18th-19th March 2010, Bethesda, USA

II. Systematic Reviews:

1. Rylance J, Pai M, Lienhardt C, Garner P. Priorities for tuberculosis research: a systematic review. *Lancet Infectious Diseases*, 2010. 10(12): 889–892
2. Pai M, Brunet L, Minion J, Steingart K, Ramsay A, Lienhardt C. Mapping the landscape and quality of TB diagnostic research. 2009.
3. Cobelens F. A Systematic Review on Operational Research studies in TB, 2011.
4. Pai M. A Systematic Review of results of systematic reviews of TB control tools.

The EGM and workshop reports as well as systematic reviews are available on: <http://www.stoptb.org/global/research/papers.asp>

Annex IV

Details of methods and analyses used to prioritize research questions

Participants and participation rate

All members were invited to comment on the first draft of the TB research roadmap, especially on the research priorities and questions listed in the document, and to participate in prioritizing the research questions in their respective area(s) of expertise. A total of 46 of the 51 invited experts (90%) completed prioritization of the research questions. The distribution of the number of contributions in the different research areas was:

Fundamental research	25
Diagnostics	21
Treatment	21
Vaccines	15
Epidemiology, operational research and public health	23

The members of the core group and the expert advisory group are listed in **Annex I**.

Method of evaluation

Each of the five sections was evaluated separately. We used two methods to evaluate the results: ‘score proportions’ analysis and ‘principal component’ analysis. There was strong overall agreement between the results of the two evaluation methods, and few apparent discrepancies were detected.

The ‘score proportion’ analysis

For each research question in each research area, the average overall score for the four priority criteria (‘efficacy and effectiveness’, ‘deliverability’, ‘equitability’, ‘answerability’) was calculated. The total number of scores (‘not’, ‘probably not’, ‘probably’ and ‘definitely’) for each of the four priority criteria was then calculated, and questions were assigned to one of three categories: (1) questions with an excess of ‘definitely’ scores over ‘not/probably not’; (2) questions with the same amount of ‘not/probably not’ and ‘definitely’ scores; and (3) questions with an excess of ‘not/probably not’ scores over ‘definitely’ scores

In a second step, the questions were further assessed according to responses to the ‘necessity’ criterion. If a majority of the respondents judged a question to be ‘rate-critical’, it was given a higher score and labelled ‘rate-critical’. If a majority of the respondents evaluated the question as ‘rate-limiting’, it was assigned a lower score and was categorized as ‘rate-limiting’. The last category contained questions that were neither rate-critical nor rate-limiting. We then combined the results of the two steps using the algorithm in **Figure 3** and assigned the questions to one of six categories (category 1, highest priority and rate-critical; 6, medium priority and neither rate-critical nor rate-limiting). Questions in categories 1 and 2 were considered to be of highest priority, questions in categories 3 and 4 of high priority and questions in categories 5 and 6 of medium priority.

This categorization was carried out for all research areas except epidemiological, public health and operational research, which was considered a priori unlikely to be rate-critical, as it is further down the value chain of research towards impact and is not critical to further essential research questions. Therefore, research questions in this area were simply categorized as of ‘highest’, ‘high’ or ‘medium’ priority after the first step.

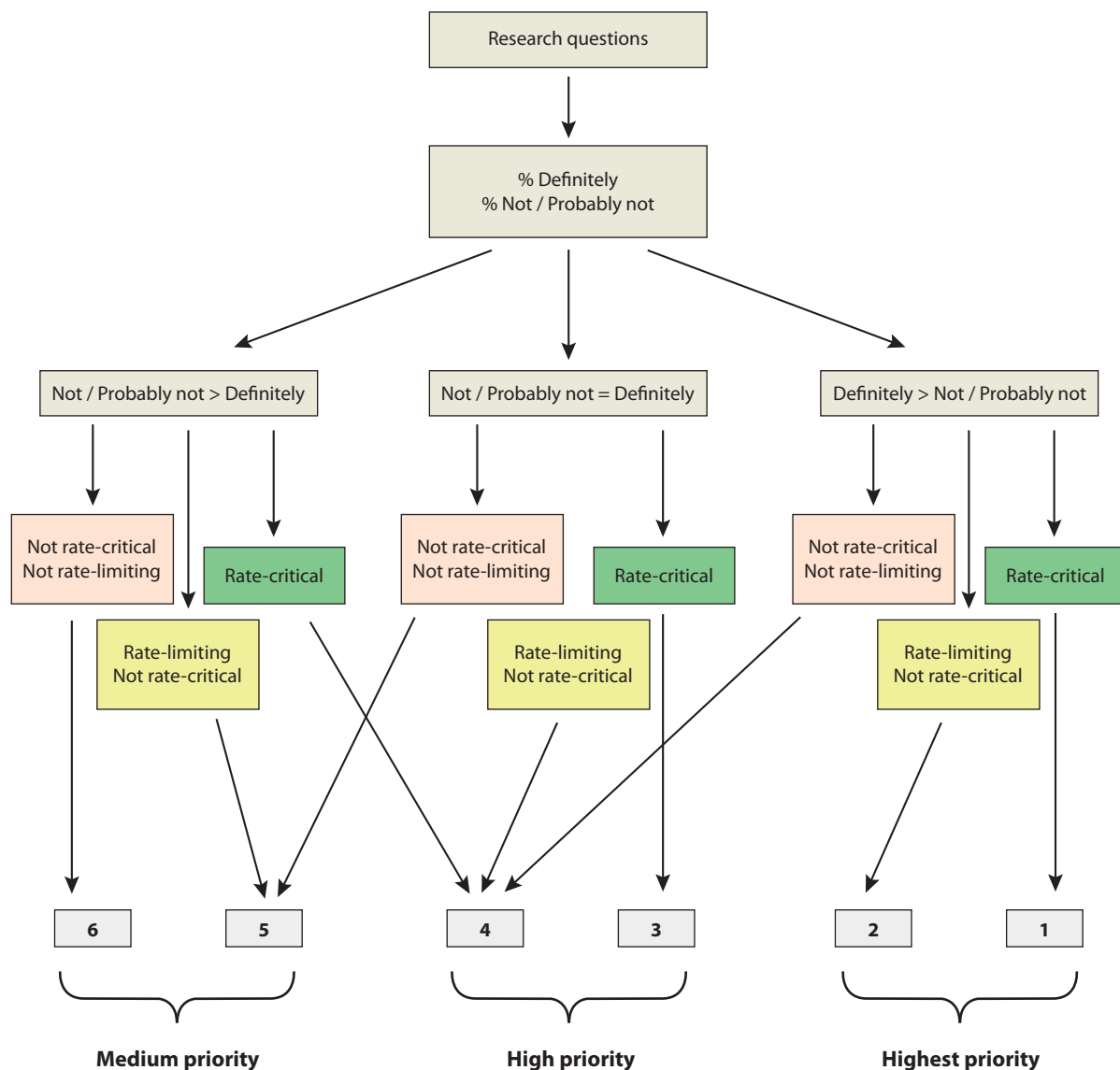
The principal component analysis

For each research question in each research area, an average score was calculated for all respondents for each of the four priority criteria: efficacy and effectiveness, deliverability, equitability and answerability. The four average scores were then combined by one of two methods to obtain an overall weighted average of the four scores for that research question. By ranking all the questions in the research area on this weighted average, the questions were split into three terciles (at the 33rd and 67th percentiles), giving three equal groups of research questions corresponding to highest, high and medium priority.

The two methods for combining the four average scores into an overall score were:

1. The simple average of the four scores assigns equal weights to the four criteria and is the most appropriate if it is considered a priori that the four criteria are equally important.
2. The weighted average (where the weights correspond to the first eigenvector or component from a principal components analysis of the covariance matrix of the four scores, calculated across all research questions in the research area) gives the weighted average with minimum variance, hence providing better discrimination among questions.

FIGURE 3. Categorization of scored research questions into three categories: ‘highest priority’ (categories 1 and 2), ‘high priority’ (categories 3 and 4) and ‘medium priority’ (categories 5 and 6)



The principal components analysis was considered to be appropriate, as the standard deviations of the four scores were small for all five research areas; hence, maximizing the discriminatory potential was considered to be important. Concordance between the two methods was assessed for all five research areas.

The 'necessity' criterion was taken into consideration, as in the score proportion analysis: if more respondents judged a question to be rate-critical, the question was categorized as rate-critical. If fewer or the same number of participants judged a question to be rate-critical, the question was not categorized as rate-critical. The same process was used to decide whether the question was rate-limiting or neither.

For the four areas of fundamental research, vaccines, treatment and diagnostics, the grouping of research questions as highest, high or medium priority was then combined with its 'necessity' with the algorithm shown in **Figure 3** into one of the six final categories (category 1, highest priority and rate-critical; 6, medium priority and neither rate-critical nor rate-limiting). As above, it was considered a priori that operational research was unlikely to be rate-critical, and so these research questions were simply grouped as of highest, high or medium priority. This a priori decision was validated, as only 2 of 54 research questions in this section were judged to be rate-critical.

The results of the two evaluations and scoring analyses are presented in **Annexes V** (result of the 'score proportions' analysis) and **VI** (results of the 'principal component' analysis), which are posted on the Stop TB Partnership Research Movement website.